AUROBINDO P1500590

LAMIVUDINE 150 mg, ZIDOVUDINE 300 mg, NEVIRAPINE 200 mg TABLETS
Rx only

AUROBINDO

PRESCRIBING INFORMATION

LAMIVUDINE 150 mg, ZIDOVUDINE 300 mg, NEVIRAPINE 200 mg TABLETS

WARNINGS:

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).

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV AND HAVE DISCONTINUED LAMIVUDINE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW- UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVUDINE AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

SEVERE, LIFE-THREATENING, AND IN SOME CASES FATAL HEPATOTOXICITY, PARTICULARLY IN THE FIRST 18 WEEKS, HAS BEEN REPORTED IN PATIENTS TREATED WITH NEVIRAPINE. IN SOME CASES, PATIENTS PRESENTED WITH NON-SPECIFIC PRODROMAL SIGNS OR SYMPTOMS OF HEPATITIS AND PROGRESSED TO HEPATIC FAILURE. THESE EVENTS ARE OFTEN ASSOCIATED WITH RASH. FEMALE GENDER AND HIGHER CD4 COUNTS AT INITIATION OF THERAPY PLACE PATIENTS AT INCREASED RISK; WOMEN WITH CD4 COUNTS >250 CELLS/MM^3, INCLUDING PREGNANT WOMEN RECEIVING NEVIRAPINE IN COMBINATION WITH OTHER ANTIRETROVIRALS FOR THE TREATMENT OF HIV INFECTION, ARE AT THE GREATEST RISK. HOWEVER, HEPATOTOXICITY ASSOCIATED WITH NEVIRAPINE USE CAN OCCUR IN BOTH GENDERS, ALL CD4 COUNTS AND AT ANY TIME DURING TREATMENT. PATIENTS WITH SIGNS OR SYMPTOMS OF HEPATITIS, OR WITH INCREASED TRANSAMINASES COMBINED WITH RASH OR OTHER SYSTEMIC SYMPTOMS, MUST DISCONTINUE LAMIVUDINE, NEVIRAPINE, ZIDOVUDNE FIXED DOSE TABLETS AND SEEK MEDICAL EVALUATION IMMEDIATELY (SEE WARNINGS).

SEVERE, LIFE-THREATENING SKIN REACTIONS, INCLUDING FATAL CASES, HAVE OCCURRED IN PATIENTS TREATED WITH NEVIRAPINE. THESE HAVE INCLUDED CASES OF STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, AND HYPERSENSITIVITY REACTIONS CHARACTERIZED BY RASH, CONSTITUTIONAL FINDINGS, AND ORGAN DYSFUNCTION. PATIENTS DEVELOPING SIGNS OR SYMPTOMS OF SEVERE SKIN REACTIONS OR HYPERSENSITIVITY REACTIONS MUST DISCONTINUE LAMIVUDINE, NEVIRAPINE AND ZIDOVUDINE FIXED DOSE TABLETS AND SEEK MEDICAL EVALUATION IMMEDIATELY.

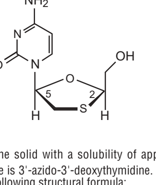
IT IS ESSENTIAL THAT PATIENTS BE MONITORED INTENSIVELY DURING THE FIRST 18 WEEKS OF THERAPY WITH NEVIRAPINE CONTAINING DRUG PRODUCTS TO DETECT POTENTIALLY LIFE-THREATENING HEPATOTOXICITY OR SKIN REACTIONS. EXTRA VIGILANCE IS WARRANTED DURING THE FIRST 6 WEEKS OF THERAPY, WHICH IS THE PERIOD OF GREATEST RISK OF THESE EVENTS. DO NOT RESTART NEVIRAPINE CONTAINING PRODUCTS FOLLOWING SEVERE HEPATIC, SKIN OR HYPERSENSITIVITY REACTIONS. IN SOME CASES, HEPATIC INJURY HAS PROGRESSED DESPITE DISCONTINUATION OF TREATMENT.

ZIDOVUDINE HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE. PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

DESCRIPTION

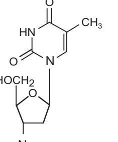
Lamivudine, Zidovudine and Nevirapine Tablets: Lamivudine, Zidovudine and Nevirapine Fixed Dose tablets are a combination of lamivudine USP (also known as 3TC), nevirapine USP and zidovudine USP. Lamivudine and Zidovudine are synthetic nucleoside analogues with activity against human immunodeficiency virus (HIV). Nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are for oral administration containing 150 mg of Lamivudine USP, 200 mg of Nevirapine USP and 300 mg of Zidovudine USP as active ingredients. Inactive ingredients include: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, povidone, lactose monohydrate, and opadry white (made of hypromellose, titanium dioxide, polyethylene glycol and polysorbate).

Lamivudine: The chemical name of lamivudine is(-)-1-[(2*R*,5S)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine. 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 229.26. It has the following structural formula:



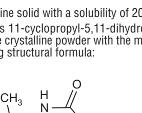
Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20^{o}C.

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. It has the following structural formula:



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

Nevirapine: The chemical name of nevirapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido [3,2-b:2',3'-e][1,4] diazepin-6-one. Nevirapine is a white to off-white crystalline powder with the molecular weight of 266.30 and the molecular formula $C_{15}H_{14}N_4O$. Nevirapine has the following structural formula:



Nevirapine is a white to off-white crystalline solid with a solubility of approximately 0.05 mg/mL in water at 25^{o}C.

MICROBIOLOGY

Mechanism of Action:

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue. L-TP is a weak inhibitor of mammalian DNA polymerases α and β, and mitochondrial DNA polymerase γ.

Zidovudine: Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3'-hydroxy (-OH) group is replaced by an azido (-N_3) group. Within the cells, zidovudine is converted to the active metabolite, zidovudine 5'-triphosphate (AztTP), by the sequential action of the cellular enzyme. Zidovudine 5'-triphosphate inhibits the activity of the HIV reverse transcriptase both by competing for utilization with the natural substrate, deoxythymidine 5'-triphospate (dTTP), and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite AztTP is also a weak inhibitor of the cellular DNA polymerase-α and mitochondrial polymerase-γ and has been reported to be incorporated into the DNA of cells in culture.

Nevirapine: Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. It binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ,or δ) are not inhibited by nevirapine.

Antiviral Activity In Vitro:

Lamivudine: *In vitro* activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. IC_{50} values (50% inhibitory concentrations) were in the range of 2 nM to 15 µM. Lamivudine had anti-HIV-1 activity in all acute virus-cell infections tested. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Zidovudine: *In vitro* activity of zidovudine against HIV-1 was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were 0.003 to 0.013 and 0.03 to 0.13 µg/mL, respectively (1 nM = 0.27 ng/mL). The IC_{50} and IC_{90} values of HIV isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 µg/mL and 0.03 to 0.3 µg/mL, respectively. Zidovudine showed antiviral activity in all acutely infected cell lines; however, activity was substantially less in chronically infected cell lines. In drug combination studies with zalcitabine, didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine, delavirdine, or interferon-alpha, zidovudine showed additive to synergistic activity in cell culture.

Nevirapine: The *in vitro* antiviral activity of nevirapine was measured in peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. IC_{50} values (50% inhibitory concentration) ranged from 10-100 nM against laboratory and clinical isolates of HIV-1. In cell culture, nevirapine demonstrated additive to synergistic activity against HIV-1 in drug combination regimens with the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine (ZDV), didanosine (ddI), stavudine (d4T), lamivudine (3TC), and the protease inhibitors saquinavir, and indinavir.

Drug Resistance:

Lamivudine Plus Zidovudine Administered As Separate Formulations: In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple mutations, the most essential of which may be at codon 333 (Gly → Glu). The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected *in vitro*. Genotypic analysis showed that the resistance was due to specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing from methionine residue to either isoleucine or valine.

Mutations in the HBV polymerase YMDD motif have been associated with reduced susceptibility of HBV to lamivudine *in vitro*. In studies of non-HIV-infected patients with chronic hepatitis B, HBV isolates with YMDD mutations were detected in some patients who received lamivudine daily for 6 months or more, and were associated with evidence of diminished treatment response; similar HBV mutants have been reported in HIV-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus (see **PRECAUTIONS**).

Zidovudine: HIV isolates with reduced sensitivity to zidovudine have been selected *in vitro* and were also recovered from patients treated with zidovudine. Genotypic analyses of the isolates showed mutations, which result in 5 amino acid substitutions (Met41→Leu, Asp67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) in the HIV-1 reverse transcriptase gene. In general, higher levels of resistance were associated with greater number of mutations.

Nevirapine: HIV-1 isolates with reduced susceptibility (100-250-fold) to nevirapine emerge *in vitro*. Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance *in vitro* was not altered when selection included nevirapine in combination with several other NNRTIs.

Phenotypic and genotypic changes in HIV-1 isolates from patients receiving either nevirapine (n=24) or nevirapine and zidovudine were monitored in Phase I/II trials over 1 to ≥12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine *in vitro*; one or more of the RT mutations K103N, V106A, V108I, Y181C, Y188C and G190A were detected in HIV-1 isolates from some patients as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the patients tested (n=24) had HIV-1 isolates with a >100-fold decrease in susceptibility to nevirapine *in vitro* compared to baseline, and had one or more of the nevirapine-associated RT resistance mutations; 19 of 24 patients (80%) had isolates with Y181C mutations regardless of dose.

Genotypic analysis of isolates from antiretroviral naïve virologic failure patients (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine (study 2NN) for 48 weeks showed that isolates from 8/25 and 23/46 patients, respectively, contained one or more of the following NNRTI resistance-associated mutations: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

Cross-Resistance*:*

Lamivudine Plus Zidovudine: Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a mutation at codon 184, which confers resistance to lamivudine. In the presence of the 184 mutation, cross-resistance to didanosine and zalcitabine has been seen in some patients; the clinical significance is unknown. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below).

Lamivudine: Lamivudine-resistant HIV-1 mutants were cross resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

In one clinical study comparing an antiretroviral regimen containing once daily lamivudine to a regimen containing twice daily lamivudine, 53/554 (10%) patients were identified as virological failures (plasma HIV-1 RNA level 400 copies/mL) by Week 48. Of the 53 failures 28 had been randomized to lamivudine once-daily and 25 to lamivudine twice-daily. Genotypic analysis of on-therapy isolates from 22 patients in the lamivudine twice-daily treatment group showed:

- isolates from 1/22 patients contained treatment-emergent zidovudine resistance mutations (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E)
- isolates from 7/22 contained treatment-emergent efavirenz resistance mutations (L100I, K101E, K103N, V108I, or Y181C)
- isolates from 5/22 contained treatment-emergent lamivudine resistance mutations (M184I or M184V)

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from 13 patients receiving lamivudine twice daily showed:

- isolates from all 13 patients were susceptible to zidovudine
- isolates from 3/13 patients exhibited a 21- to 342-fold decrease in susceptibility to efavirenz
- isolates from 4/13 patients exhibited a 29- to 159-fold decrease in susceptibility to lamivudine

Zidovudine: The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Combination therapy with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of zidovudine-resistant isolates. Combination therapy with zidovudine plus lamivudine delayed the emergence of mutations conferring resistance to zidovudine. In some patients harboring zidovudine-resistant virus, combination therapy with zidovudine plus lamivudine restored phenotypic sensitivity to zidovudine by 12 weeks of treatment. HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for ≥1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile, Phe77→116Tyr, and Gln1→51Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine.

Nevirapine: Rapid emergence of HIV-1 strains which are cross-resistant to NNRTIs has been observed *in vitro*. Nevirapine-resistant HIV-1 isolates were cross-resistant to the NNRTIs delavirdine and efavirenz. However, nevirapine-resistant isolates were susceptible to the nucleoside analogues ZDV and ddI. Similarly, ZDV-resistant isolates were susceptible to nevirapine *in vitro*.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults:

Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets:

Aurobindo Combination Fixed Dose Tablets containing Lamivudine 150 mg, Zidovudine 300 mg, and Nevirapine 200 mg are bioequivalent to Epivir® tablets (lamivudine) 150 mg (GlaxoSmithKline, Research Triangle Park, NC 27709), Retrovir® tablets (zidovudine) 300 mg (GlaxoSmithKline, Research Triangle Park, NC 27709), and Viramune® tablets (nevirapine) 200 mg (manufactured by Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT 06877, USA) when the three single entity tablets are given together in a single dose to healthy volunteers under fasting conditions. The Aurobindo Combination Fixed Dose Tablets dosed under fed conditions (high fat, high calorie meal) are also bioequivalent to the three single entity tablets given together under the same fed conditions to healthy volunteers.

Lamivudine:

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-infected adult patients after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg/kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5 mg to 600 mg/day administered to HBV-infected patients.

Absorption and Bioavailability: Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150 mg tablet. After oral administration of 2 mg/kg twice a day to 9 adults with HIV, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 µg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.

An investigational 25 mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-infected patients on 2 occasions, once in the fasted state and once with food. Absorption of lamivudine was slower in the fed state (T_{max}: 3.2 ± 1.3 hours) compared with the fasted state (T_{max}: 0.9 ± 0.3 hours); C_{max} in the fed state was 40% ± 23% (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposures (AUC_∞) in the fed and fasted states; therefore, lamivudine may be administered with or without food.

The accumulation ratio of lamivudine in HIV-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

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

Metabolism: Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Elimination: The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300 mg oral dose of lamivudine, renal clearance was 199.7±56.9 mL/min (mean±SD). In 20 HIV-infected patients given a single IV dose, renal clearance was 280.4±75.2 mL/min (mean±SD), representing 71%±16% (mean±SD) of total clearance of lamivudine.

In most single-dose studies in HIV-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

Zidovudine:

Following oral administration, zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0.5 to 1.5 hours. Binding to plasma protein is low. Zidovudine is primarily eliminated by hepatic metabolism. The major metabolite of zidovudine is 3'-azido-3'-deoxy-5'-O-ß-D-glucopyranuronosylthymidine (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%, respectively, of the dose following oral administration. A second metabolite, 3'-amino- 3'-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous (IV) administration of zidovudine. The AMT AUC was one fifth of the zidovudine AUC. Pharmacokinetics of zidovudine were dose independent at oral dosing regimens ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

Zidovudine pharmacokinetic parameters in fasting adult patients*

Parameter	Zidovudine
Oral bioavailability (%)	64 ± 10
Apparent volume of distribution (L/kg)	1.6 ± 0.6
Plasma protein binding (%)	<38
CSF: plasma ratio	0.6 [0.04 to 2.62]
Systemic clearance (L/hr/kg)	1.6 ± 0.6
Renal clearance (L/hr/kg)	0.34 ± 0.05
Elimination half-life (hr)†	0.5 to 3

*Data presented as mean ± standard deviation except where noted.

†Approximate range.

The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine was administered with food. Zidovudine may be administered with or without food.

Nevirapine:

Absorption and Bioavailability: Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in healthy adults following single-dose administration was 93 ± 9% (mean ± SD) for a 50 mg tablet. Peak plasma nevirapine concentrations of 2 ± 0.4 µg/mL (7.5 µM) are attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5 ± 1.9 µg/mL (17 ± 7 µM), are attained at 400 mg/day. The absorption of nevirapine is not affected by food, antacids or ddI. Hence, nevirapine may be administered with or without food, antacids or ddI.

Distribution: Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. In healthy adults, the apparent volume of distribution (Vdss) of nevirapine is 1.21 ± 0.09 L/kg after intravenous administration, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is also found in breast milk (see **PRECAUTIONS, Nursing Mothers**). Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 µg/mL. Nevirapine concentrations in human cerebrospinal fluid are 45% (± 5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

Metabolism/Elimination: *In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A4 and CYP2B6 families, although other isozymes may have a secondary role. In healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of ^{14}C-nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

Nevirapine is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A4 and 2B6. Nevirapine induces CYP3A4 and CYP2B6 by approximately 20-25%, as indicated by erythromycin breath test results and urine metabolites. Autoinduction of CYP3A4 and CYP2B6 mediated metabolism leads to an approximately 1.5 to 2 fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma, from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

Effect of Food on Absorption of lamivudine, zidovudine and nevirapine tablets: Lamivudine, zidovudine and nevirapine fixed dose tablets may be administered with or without food. The extent of lamivudine, zidovudine, and nevirapine absorption (AUC) following administration of lamivudine, zidovudine and nevirapine tablets with food was similar when compared to across studies fasting healthy subjects (n = 34). These results are similar to those from previous studies of the effect of food on lamivudine, zidovudine, and nevirapine tablets administered separately.

Special Populations:

Pediatrics

Adjustment of the dose of lamivudine, nevirapine or zidovudine is not possible with this fixed dose combination. Therefore, Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are not recommended for patients <12 years of age or those who weigh <50 kg.

Impaired Renal Function

Because dose adjustments are not possible, Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are not recommended for use in patients with creatinine clearance <50 mL/min.

Hepatic Impairment

Because dose adjustments are not possible, Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are not suitable for patients with any degree of hepatic impairment.

Geriatric

Lamivudine and Zidovudine: Pharmacokinetics of either drug have not been studied in patients > 65 years of age (see **PRECAUTIONS**).

Nevirapine: Nevirapine pharmacokinetics in HIV-1 infected adults does not appear to change with age (range 18 to 68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 55 years.

Gender

Lamivudine: There are no significant gender differences in lamivudine pharmacokinetics.

Zidovudine: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no differences in zidovudine exposure (AUC) when a single dose of zidovudine was administered as the 300-mg zidovudine tablet.

Nevirapine: In one Phase I study in healthy volunteers (15 females, 15 males), the weight-adjusted apparent volume of distribution (Vdss/F) of nevirapine was higher in the female subjects (1.54 L/kg) compared to the males (1.38 L/kg), suggesting that nevirapine was distributed more extensively in the female subjects. However, this difference was offset by a slightly shorter terminal-phase half-life in the females resulting in no significant gender difference in nevirapine oral clearance (24.6±7.7 mL/kg/hr in females vs. 19.9±3.9 mL/kg/hr in males after single dose) or plasma concentrations following either single- or multiple-dose administration(s).

Race

Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics.

Nevirapine: An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1 infected patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median C_{minss} = 4.7 µg/mL Black, 3.8 µg/mL Hispanic, 4.3 µg/mL Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

Drug Interactions: See **PRECAUTIONS.**

INDICATIONS AND USAGE

Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets are indicated for patients > 12 years of age and those weighing >50 kg for the treatment of HIV-1 infection, alone or in combination with other antiretroviral agents.

Additional Important Information regarding the use of Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets:

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets should not be initiated in adult females with CD4+ cell counts greater than 250 cells/mm^3 or in adult males with CD4+ cell counts greater than 400 cells/mm^3 unless the benefit outweighs the risk (see **WARNINGS**).
- A 14-day lead-in period with nevirapine 200 mg once daily dosing, given with other antiretrovirals, has been demonstrated to reduce the frequency of rash (see **WARNINGS; DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets are contraindicated in patients with clinically significant hypersensitivity to any of the components of the product.

Description of Clinical Studies:

Lamivudine, zidovudine and nevirapine tablets: There have been no clinical trials conducted with the fixed dose combination tablets. See **CLINICAL PHARMACOLOGY** for information about bioequivalence of the fixed dose combination.

WARNINGS

Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets should not be administered concomitantly with formulations containing any of the three drugs. The complete prescribing information for all agents being considered for use with Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets should be consulted before combination therapy with Lamivudine, Zidovudine and Nevirapine tablets is initiated.

Use with Interferon and Ribavirin-Based Regimens: *In vitro* studies have shown ribavirin can reduce the phosphorylation of nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) interaction was seen when ribavirin was co-administered with lamivudine *and/or* zidovudine in HIV/HCV co-infected patients (see **PRECAUTIONS-*Drug Interactions***). Hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon and ribavirin. Patients receiving *interferon with or without ribavirin* and *lamivudine and/or zidovudine* should be closely monitored for treatment associated toxicities, especially hepatic decompensation, neutropenia and anemia. Discontinuation of Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets should be considered as medically appropriate. Dose reduction or discontinuation of interferon, ribavirin or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh > 6). See the complete prescribing information for interferon and ribavirin products.

Lamivudine and Zidovudine

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine and other antiretrovirals. A majority of these cases have been in women. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of zidovudine and didanosine with other antiretroviral agents. The combination of zidovudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see **PRECAUTIONS - Pregnancy**).

Particular caution should be exercised when administering lamivudine and zidovudine to any patient with known risk factors for liver disease; however, cases of lactic acidosis have also been reported in patients with no known risk factors. Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness) might be indicative of lactic acidosis development.

Treatment with Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of symptomatic hyperlactatemia, lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Lamivudine

Post-treatment Exacerbations of Hepatitis: In clinical trials in non-HIV-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 re-emergence of hepatitis B viral DNA (HBV DNA). Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV 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.

Pancreatitis: In pediatric patients with a history of prior antiretroviral exposure, a history of pancreatitis, or other significant risk factor for the development of pancreatitis, lamivudine should be used with caution. Treatment with Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see **ADVERSE REACTIONS**).

Nevirapine

General: The most serious adverse reactions associated with nevirapine are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be associated with signs of hypersensitivity which can include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction.

The first 18 weeks of therapy with nevirapine are a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life threatening hepatic events and skin reactions. The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation and at two weeks post-dose escalation. After the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment. In addition, the 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash (see **DOSAGE AND ADMINISTRATION)**.

Hepatic Events: Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with nevirapine. In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11.0%) of patients who received nevirapine and 1.2% of patients in control groups.

The risk of symptomatic hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the nevirapine groups compared to controls through 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately half of the patients with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Patients with signs or symptoms of hepatitis must be advised to discontinue Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets and immediately seek medical evaluation, which should include liver function tests.

Liver function tests should be performed immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Liver function tests should also be obtained immediately for all patients who develop a rash in the first 18 weeks of treatment. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if liver function tests are initially normal or alternative diagnoses are possible (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets should be permanently discontinued. Do not restart Lamivudine,Zidovudine and Nevirapine Fixed Dose Tablets after recovery. In some cases, hepatic injury progresses despite discontinuation of treatment.

The patients at greatest risk of hepatic events, including potentially fatal events, are women with high CD4 counts. In general, during the first 6 weeks of treatment, women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4 counts >250 cells/mm^3 had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts <250 cells/mm^3 (11.0% versus 0.9%). An increased risk was observed in men with CD4 counts >400 cells/mm^3 (6.3% versus 1.2% for men with CD4 counts <400 cells/mm^3). However, all patients, regardless of gender, CD4 count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4 counts. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-uninfected individuals receiving multiple doses of nevirapine in the setting of post-exposure prophylaxis, an unapproved use.

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets should not be administered to patients with severe hepatic impairment (see **Pharmacokinetics in Special Populations: Hepatic Impairment**).

Skin Reactions: Severe and life-threatening skin reactions, including fatal cases, have been reported, occurring most frequently during the first 6 weeks of therapy. These have included cases of Stevens- Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction including hepatic failure. In controlled clinical trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 1.5% of nevirapine recipients compared to 0.1% of placebo subjects.

Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets and seek medical evaluation immediately (see **PRECAUTIONS**). Do not restart Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

If patients present with a suspected nevirapine-associated rash, liver function tests should be performed. Patients with rash-associated AST or ALT elevations should be permanently discontinued from Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets.

Therapy with nevirapine must be initiated with a 14-day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients), which has been shown to reduce the frequency of rash. If rash is observed during the lead-in period, dose escalation should not occur until the rash has resolved. Patients should be monitored closely if isolated rash of any severity occurs. Delay in stopping nevirapine containing treatment after the onset of rash may result in a more serious reaction.

Women appear to be at higher risk than men of developing rash with nevirapine.

In a clinical trial, concomitant prednisone use (40 mg/day for the first 14 days of nevirapine administration) was associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine therapy. Therefore, use of prednisone to prevent nevirapine -associated rash is not recommended.

Resistance: When discontinuing an antiretroviral regimen containing nevirapine, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than nevirapine are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop.

St. John's Wort: Concomitant use of St. John's wort (hypericum perforatum) or St. John's wort containing products and nevirapine is not recommended. Co-administration of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), including nevirapine, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in sub-optimal levels of nevirapine and lead to loss of virologic response and possible resistance to nevirapine or to the class of NNRTIs.

Zidovudine:

Bone Marrow Suppression:

The major toxicities of zidovudine are neutropenia and anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection. Zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm3 or hemoglobin <9.5 g/dL. Zidovudine-related hematologic toxicities appear related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia. In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks. If anemia or neutropenia develops discontinuation of Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets and/or blood transfusion may be warranted. Dose adjustments for zidovudine are not recommended for hematologic toxicities because the dosage from and strength of the zidovudine component of the fixed dose tablets are not appropriate for dose adjustments. (see **DOSAGE AND ADMINISTRATION**). Instead, dose interruption, dose discontinuation and/or blood transfusions may be warranted to manage serious anemia.

Myopathy: Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of zidovudine.

PRECAUTIONS

Lamivudine, Zidovudine and Nevirapine:

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.

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

Patients with Impaired Renal Function: **Because dose adjustments are not possible, Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets are not recommended for use in patients with creatinine clearance <50 mL/min.**

Patients with Impaired Hepatic Function: **Because dose adjustments are not possible, Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets are not suitable for patients with any degree of hepatic impairment.**

Information for Patients

The Medication Guide provides written information for the patient, and should be dispensed with each new prescription and refill.

Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets are not a cure for HIV infection. Patients should be advised of the importance of taking lamivudine, zidovudine and nevirapine fixed dose tablets on a regular dosing schedule and to avoid missing doses.

Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV-associated diseases. Patients should be advised that the use of antiretroviral therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be informed 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.

Lamivudine: Patients co-infected with HIV and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician. Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis.

Nevirapine: **Patients should be informed of the possibility of severe liver disease or skin reactions associated with nevirapine that may result in death. Patients developing signs or symptoms of liver disease or severe skin reactions should be instructed to discontinue Lamivudine, Zidovudine or Nevirapine Fixed Dose Tablets and seek medical attention immediately, including performance of laboratory monitoring. Symptoms of liver disease include fatigue, malaise, anorexia, nausea, jaundice, acholic stools, liver tenderness or hepatomegaly. Symptoms of severe skin or hypersensitivity reactions include rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema and/or hepatitis.**

Patients should be advised that co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT (see **WARNINGS, Hepatic Events**).

Patients should be instructed that if any rash occurs during the two-week lead-in period, the nevirapine dose should not be escalated until the rash resolves. Any patient experiencing a rash should have their liver function evaluated immediately. Patients with severe rash or hypersensitivity reactions should discontinue Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets immediately and consult a physician. Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets should not be restarted following severe skin rash or hypersensitivity reaction. Women tend to be at higher risk for development of nevirapine associated rash.

Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets, since nevirapine may lower the plasma levels of these medications. Additionally, when oral contraceptives are used for hormonal regulation during Lamivudine,Zidovudine and Nevirapine Fixed Dose Tablets therapy, the therapeutic effect of the hormonal therapy should be monitored.

Based on the known metabolism of methadone, nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Nevirapine may interact with some drugs, therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients should be informed to take Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets every day as prescribed. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose. Patients should be advised to report to their doctor the use of any other medications.

Zidovudine: Patients should be informed that the major toxicities of zidovudine are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection. They should be told that if toxicity develops, they may require transfusions or drug discontinuation. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV disease. They should be cautioned about the use of other medications, including ganciclovir and interferon-alpha that may exacerbate the toxicity of zidovudine (see **PRECAUTIONS: Drug Interactions**). Patients should be informed that other adverse effects of zidovudine include nausea and vomiting. Patients should also be encouraged to contact their physician if they experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being treated with zidovudine.

Pregnant women considering the use of zidovudine during pregnancy should be advised that transmission may still occur in some cases despite therapy. The long-term consequences of *in utero* and infant exposure to zidovudine are unknown, including the possible risk of cancer. HIV-infected pregnant women should be advised not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected.

Drug Interactions:

Lamivudine: Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).

Lamivudine and trimethoprim/sulfamethoxazole (TMX/SMX) were coadministered to 14 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 44% ± 23% (mean ± SD) in lamivudine AUC_∞, a decrease of 29% ±13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine.

There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat *Pneumocystis carinii* pneumonia. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

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

Zidovudine: See Table 1 for information on zidovudine concentrations when co-administered with other drugs. For patients experiencing pronounced anemia or other severe zidovudine-associated events while receiving chronic administration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 1, zidovudine dose reduction may be considered.

Table 1: Effect of Coadministered Drugs on Zidovudine AUC*

Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations: AUC	Zidovudine Concentrations: Variability	Concentration of Coadministered Drug
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 (cont) 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%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130%†	Not Assessed

↑ = 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.

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

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

Phenytoin: Phenytoin plasma levels have been reported to be low in some patients receiving zidovudine while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

Use with Interferon- and Ribavirin-Based Regimens: No evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine or zidovudine. However, HIV/HCV co-infected patients who were administered zidovudine, in combination with pegylated interferon and ribavirin developed severe neutropenia (ANC <500) and severe anemia (hemoglobin <8 g/dL) more frequently than similar patients not receiving zidovudine (neutropenia 15% vs. 9%, anemia 5% vs. 1%).

Overlapping Toxicities: Coadministration of ganciclovir, interferon-$\propto$, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Nevirapine: Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A4 and 2B6. Nevirapine is known to be an inducer of these enzymes. Co-administration of nevirapine-containing products and drugs primarily metabolized by CYP3A4 or CYP2B6 may result in decreased plasma concentrations of these drugs and attenuate their therapeutic effects.

While primarily an inducer of cytochrome P450 3A4 and 2B6 enzymes, nevirapine may also inhibit this system. Among human hepatic cytochrome P450s, nevirapine was capable *in vitro* of inhibiting the 10-hydroxylation of (R)-warfarin (CYP3A4). The estimated K_i for the inhibition of CYP3A4 was 270 µM, a concentration that is unlikely to be achieved in patients as the therapeutic range is <25 µM. Therefore, nevirapine may have minimal inhibitory effect on other substrates of CYP3A4.

Nevirapine does not appear to affect the plasma concentrations of drugs that are substrates of other CYP450 enzyme systems, such as 1A2, 2D6, 2A6, 2E1, 2C9 or 2C19.

The Table below contains the results of drug interaction studies performed with nevirapine and other drugs likely to be co-administered. The effects of nevirapine on the AUC, C_{max}, and C_{min} of co-administered drugs are summarized. To measure the full potential pharmacokinetic interaction effect following induction, patients on the concomitant drug at steady state were administered 28 days of nevirapine (200 mg QD for 14 days followed by 200 mg BID for 14 days) followed by a steady state reassessment of the concomitant drug.

Table 2: Changes in Pharmacokinetic Parameters For Co-administered Drug in The Presence of

ATTENTION PHARMACISTS: Detach "Medication Guide" and dispense with the product.

MEDICATION GUIDE

LAMIVUDINE 150 mg, ZIDOVUDINE 300 mg, NEVIRAPINE 200 mg TABLETS

Rx only

Read this Medication Guide before you start taking lamivudine, zidovudine and nevirapine tablets and each time you get a refill because there may be new information. This information does not take the place of talking with your doctor. You and your doctor should talk about lamivudine, zidovudine and nevirapine tablets when you start taking your medicine and at regular checkups. You should stay under a doctor's care while using lamivudine, zidovudine and nevirapine tablets. You should consult with your doctor before making any changes to your medications, except in any of the special circumstances described below regarding rash or liver problems.

What is the most important information I should know about lamivudine, zidovudine and nevirapine tablets?

Severe liver disease or skin reactions

Patients taking lamivudine, zidovudine and nevirapine tablets may develop severe liver disease or skin reactions that can cause death. The risk of these reactions is greatest during the first 18 weeks of treatment, but these reactions also can occur later.

Liver Reactions

Any patient can experience liver problems while taking lamivudine, zidovudine and nevirapine tablets. However, women and patients who have higher CD4 counts when they begin lamivudine, zidovudine and nevirapine tablets treatment have a greater chance of developing liver damage. Women with CD4 counts higher than 250 cells/mm³ are at the greatest risk of these events. If you are a woman with CD4>250 cells/mm³ or a man with CD4>400 cells/mm³ you should not begin taking lamivudine, zidovudine and nevirapine tablets unless you and your doctor have decided that the benefit of doing so outweighs the risk. Liver problems are often accompanied by a rash.

Patients starting lamivudine, zidovudine and nevirapine tablets with abnormal liver function tests and patients with hepatitis B or C have a greater chance of developing further increases in liver function tests after starting therapy with lamivudine, zidovudine and nevirapine tablets and throughout therapy.

In rare cases liver problems have led to liver failure and can lead to a liver transplant or death. Therefore, if you develop any of the following symptoms of liver problems stop taking lamivudine, zidovudine and nevirapine tablets and call your doctor right away:

- general ill feeling or "flu-like" symptoms
- tiredness
- nausea (feeling sick to your stomach)
- lack of appetite
- yellowing of your skin or whites of your eyes
- dark urine (tea colored)
- pale stools (bowel movements)
- pain, ache, or sensitivity to touch on your right side below your ribs

Your doctor should check you and do blood tests often to check your liver function during the first 18 weeks of therapy. Checks for liver problems should continue regularly during treatment with lamivudine, zidovudine and nevirapine tablets.

Skin Reactions

Skin rash is the most common side effect of nevirapine, which is one the components of lamivudine, zidovudine and nevirapine tablets. Most rashes occur in the first 6 weeks of treatment. In a small number of patients, **rash can be serious and result in death. Therefore, if you develop a rash with any of the following symptoms stop using lamivudine, zidovudine and nevirapine tablets and call your doctor right away:**

- general ill feeling or "flu-like" symptoms
- fever
- muscle or joint aches
- conjunctivitis (red or inflamed eyes, like "pink eye")
- any of the symptoms of liver problems discussed above
- blisters
- mouth sores
- swelling of your face
- tiredness

If your doctor tells you to stop treatment with lamivudine, zidovudine and nevirapine tablets because you have experienced the serious liver or skin reactions described above, never take lamivudine, zidovudine and nevirapine tablets again.

Lactic Acidosis

Some HIV medicines, including lamivudine, zidovudine and nevirapine tablets can cause a rare but serious condition called lactic acidosis with liver enlargement (hepatomegaly). Nausea and tiredness that don't get better may be symptoms of lactic acidosis. In some cases this condition can cause death. Women, overweight people, and people who have taken HIV medicines like lamivudine, zidovudine and nevirapine tablets for a long time have a higher chance of getting lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must be treated in hospital.

Worsening of hepatitis B virus (HBV) infection

Patients with HBV infection, who take lamivudine, zidovudine and nevirapine tablets and then stop them, may get "flare-ups" of their hepatitis. "Flare-up" is when the disease suddenly returns in a worse way than before. If you have HBV infection, your doctor should closely monitor your liver function for several months after stopping lamivudine, zidovudine and nevirapine tablets. You may need to take anti-HBV medicines.

Hematologic toxicity

Lamivudine, zidovudine and nevirapine tablets have been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV disease. Prolonged use of lamivudine, zidovudine and nevirapine tablets has been associated with symptomatic myopathy.

These are not all the side effects of lamivudine, zidovudine and nevirapine tablets. (See the section "What are the possible side effects of lamivudine, zidovudine and nevirapine tablets?" for more information.) Tell your doctor if you have any side effects from lamivudine, zidovudine and nevirapine tablets.

What are lamivudine, zidovudine and nevirapine tablets?

Lamivudine, zidovudine and nevirapine tablets are a prescription medicine used to treat HIV infection. They contain 3 medicines: lamivudine, zidovudine and nevirapine. See the end of this Medication Guide for a complete list of ingredients in lamivudine, zidovudine and nevirapine tablets. When used together, they help lower the amount of HIV in your blood. This helps to keep your immune system as healthy as possible so that it can help fight infection.

Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for you.

- **Lamivudine, zidovudine and nevirapine tablets do not cure HIV infection or AIDS.** We do not know if lamivudine, zidovudine and nevirapine tablets will help you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is very important that you see your doctor regularly while you are taking lamivudine, zidovudine and nevirapine tablets.
- **Lamivudine, zidovudine and nevirapine tablets do not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others, it is important to always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take lamivudine, zidovudine and nevirapine tablets?

- Do not take lamivudine, zidovudine and nevirapine tablets if you are allergic to nevirapine or any other medicine that has nevirapine as one of its ingredients (Viramune). See the end of this Medication Guide for a complete list of ingredients in lamivudine, zidovudine and nevirapine tablets.
- Do not restart lamivudine, zidovudine and nevirapine tablets after you recover from serious liver or skin reactions that happened when you took lamivudine, zidovudine and nevirapine tablets.
- Do not take lamivudine, zidovudine and nevirapine tablets if you take certain medicines. (See "Can I take other medicines with lamivudine, zidovudine and nevirapine tablets?" for a list of medicines.)
- Do not take lamivudine, zidovudine and nevirapine tablets if you are not infected with HIV.

What should I tell my doctor before taking lamivudine, zidovudine and nevirapine tablets?

Before starting lamivudine, zidovudine and nevirapine tablets, tell your doctor about all of your medical conditions, including if you:

- have problems with your liver or have had hepatitis
- are undergoing dialysis
- have skin conditions, such as a rash
- are pregnant, planning to become pregnant, or are breast feeding

We do not know if lamivudine, zidovudine and nevirapine tablets will harm your unborn child. You and your doctor will need to decide if lamivudine, zidovudine and nevirapine tablets are right for you.

If you are breast feeding, some of the ingredients in lamivudine, zidovudine and nevirapine tablets can be passed to your baby in your breast milk. It is not known if they could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.

How should I take lamivudine, zidovudine and nevirapine tablets?

- Take lamivudine, zidovudine and nevirapine tablets by mouth exactly as your

Table 2: Changes in Pharmacokinetic Parameters For Co-administered Drug in The Presence of Nevirapine (All Interaction Studies Were Conducted in HIV-1 Positive Patients)

Co-administered Drug	Dose of Co-administered drug	Dose regimen of nevirapine	n	% Change of co-administered drug Pharmacokinetic Parameters (90 % CI) AUC	C_{max}	C_{min}
Antiretrovirals						
Didanosine	100-150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	§
Efavirenz[a]	600 mg QD	200 mg QD x 14 days; 400 mg QD x 14 days	17	↓ 28 (↓ 34 to ↓ 14)	↓ 12 (↓ 23 to ↑ 1)	↓ 32 (↓ 35 to ↓ 19)
Indinavir[a]	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓ 31 (↓ 39 to ↓22)	↓ 15 (↓ 24 to ↓ 4)	↓ 44 (↓ 53 to ↓ 33)
Lopinavir[a, b]	300/75 mg/m² (lopinavir/ ritonavir) [b]	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15[c]	↓ 14 (↓ 36 to ↑ 16)	↓ 22 (↓ 44 to ↑ 9)	↓ 55 (↓ 75 to ↓ 9)
Lopinavir[a]	400/100 mg BID (lopinavir/ ritonavir)	200 mg QD x 14 days; 200 mg BID > 1 year	22, 19[c]	↓ 27 (↓ 47 to ↓ 2)	↓ 19 (↓ 38 to ↑ 5)	↓ 51 (↓ 72 to ↓ 26)
Nelfinavir[a]	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	↔	↔	↓ 32 (↓ 50 to ↑ 5)
Nelfinavir-M8 Metabolite				↓ 62 (↓ 70 to ↓ 53)	↓ 59 (↓ 68 to ↓ 48)	↓ 66 (↓ 74 to ↓ 55)
Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	↔
Saquinavir[a]	600 mg TID	200 mg QD x 14 days; 200 mg BID x 21 days	23	↓ 38 (↓ 47 to ↓ 11)	↓ 32 (↓ 44 to ↓ 6)	§
Stavudine	30-40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	↔	↔	§
Zalcitabine	0.125-0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	↔	↔	§
Zidovudine	100-200 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓ 28 (↓ 40 to ↓ 4)	↓ 30 (↓ 51 to ↑ 14)	§
Other Medications						
Clarithromycin[a]	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓ 31 (↓ 38 to ↓ 24)	↓ 23 (↓ 31 to ↓ 14)	↓ 57 (↓ 70 to ↓ 36)
Metabolite 14-OH-clarithromycin				↑ 42 (↑ 16 to ↑73)	↑ 47 (↑ 21 to ↑ 80)	↔
Ethinyl estradiol[a]	0.035 mg	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓ 20 (↓ 33 to ↓ 3)	↔	§
and Norethindrone[a]	1 mg			↓ 19 (↓ 30 to ↓ 7)	↓ 16 (↓ 27 to ↓ 3)	§
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↔	↔	↔
Ketoconazole[a]	400 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	21	↓ 72 (↓ 80 to ↓ 60)	↓ 44 (↓ 58 to ↓ 27)	§
Rifabutin[a]	150 or 300 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↑ 17 (↓ 2 to ↑ 40)	↑ 28 (↑ 9 to ↑ 51)	↔
Metabolite 5-O-desacetyl-Rifabutin				↑ 24 (↓ 16 to ↑ 84)	↑ 29 (↓ 2 to ↑ 68)	↑ 22 (↓ 14 to ↑ 74)
Rifampin[a]	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑ 11 (↓ 4 to ↑ 28)	↔	§

§ = C_{min} below detectable level of the assay

↑ = Increase, ↓ = Decrease, ↔ = No Effect

[a] For information regarding clinical recommendations see Table below

[b] Pediatric subjects ranging in age from 6 months to 12 years

[c] Parallel group design; n for nevirapine +lopinavir/ritonavir, n for lopinavir/ritonavir alone

Because of the design of the drug interaction trials (addition of 28 days of nevirapine therapy to existing HIV therapy) the effect of the concomitant drug on plasma nevirapine steady state concentrations was estimated by comparison to historical controls.

Administration of rifampin had a clinically significant effect on nevirapine pharmacokinetics, decreasing AUC and C_{max} by greater than 50%. Administration of fluconazole resulted in an approximate 100% increase in nevirapine exposure, based on a comparison to historic data. The effects of other drugs listed in above table on nevirapine pharmacokinetics were not significant.

Clinical comments about possible dosage modifications based on these pharmacokinetic changes are listed in Table 3. The data in Tables 3 and 4 are based on the results of drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

Table 3: Clinical Comments About Possible Dosage Modifications of Concomitant Drug

Drug name	Effect on concentration of Nevirapine or concomitant drug	Clinical comment
Clarithromycin	↓Clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased.
	↑ 14-OH Clarithromycin	Because clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex*, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Efavirenz	↓ Efavirenz	Appropriate doses for this combination are not established.
Ethinyl estradiol and Norethindrone	↓ Ethinyl estradiol Norethindrone	Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.
Fluconazole	↑ Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine- associated adverse events.
Indinavir	↓ Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/Ritonavir	↑ Lopinavir	A dose increase of lopinavir/ritonavir to 533/133600/150 mg twice daily (two tablets twice daily) in cwith food is recommended in combination with nevirapine may be considered in treatment experienced patients where decreased susceptibility to nevirapine is clinically suspected.
Methadone	↓ Methadone[a]	Methadone levels may be decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Nelfinavir	↓Nelfinavir M8 Metabolite ↓Nelfinavir C_{min}	The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑ Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine containing regimen may use rifabutin instead.
Saquinavir	↓ Saquinavir	Appropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.

[a] Based on reports of narcotic withdrawal syndrome in patients treated with nevirapine and methadone concurrently, and evidence of decreased plasma concentrations of methadone.

In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are listed in the table below. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in the table below, additional clinical monitoring may be warranted when co-administering these drugs.

The *in vitro* interaction between nevirapine and the antithrombotic agent warfarin is complex. As a result, when giving these drugs concomitantly, plasma warfarin levels may change with the potential for increases in coagulation time. When warfarin is co-administered with nevirapine, anticoagulation levels should be monitored frequently.

Table 4: Potential drug interactions: Use with caution, Dose adjustment of co-administered drug may be needed due to possible decrease in clinical effect

Drug class	Examples of drugs
Examples of drugs in which plasma concentrations may be decreased by co-administration with nevirapine	
Antiarrhythmics	Amiodarone, disopyramide, lidocaine
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antifungals	Itraconazole
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Cancer chemotherapy	Cyclophosphamide
Ergot alkaloids	Ergotamine
Immunosuppressants	Cyclosporin, tacrolimus, sirolimus
Motility agents	Cisapride
Opiate agonists	Fentanyl
Examples of drugs in which plasma concentrations may be increased by co-administration with nevirapine	
Antithrombotics	Warfarin Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

See **CLINICAL PHARMACOLOGY** for additional drug interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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) those observed in humans at the recommended therapeutic dose for HIV infection. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV infection.

In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

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/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/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.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Zidovudine was mutagenic in a L5178Y/TK+/- 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. 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.

Nevirapine: Long-term carcinogenicity studies in mice and rats were carried out nevirapine. Mice were dosed with 0, 50, 375 or 750 mg/kg/day for two years. Hepatocellular adenomas and carcinomas were increased at all doses in males and at the two high doses in females. In studies in which rats were administered nevirapine at doses of 0, 3.5, 17.5 or 35 mg/kg/day for two years, an increase in hepatocellular adenomas was seen in males at all doses and in females at the high dose. The systemic exposure (based on AUCs) at all doses in the two animal studies were lower than that measured in humans at the 200 mg bid dose. The mechanism of the carcinogenic potential is unknown.

In genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included microbial assays for gene mutation (Ames: Salmonella strains and *E. coli*), mammalian cell gene mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine treated mice and rats are not known.

In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of nevirapine.

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets should be used during pregnancy only if the potential benefits outweigh the risks.

Lamivudine: Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/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 that in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

In 2 clinical studies conducted in South Africa, pharmacokinetic measurements were performed on samples from pregnant women who received lamivudine beginning at week 38 of gestation (10 women who received 150 mg twice daily in combination with zidovudine and 10 who received lamivudine 300 mg twice daily without other antiretrovirals) or beginning at week 36 of gestation (16 women who received lamivudine 150 mg twice daily in combination with zidovudine). These studies were not designed or powered to provide efficacy information.

Lamivudine pharmacokinetics in the pregnant women were similar to those obtained following birth and in non-pregnant adults. Lamivudine concentrations were generally similar in maternal, neonatal, and cord serum samples. In a subset of subjects from whom amniotic fluid specimens were obtained following natural rupture of membranes, amniotic fluid concentrations of lamivudine ranged from 1.2 to 2.5 µg/mL (150 mg twice daily) and 2.1 to 5.2 µg/mL (300 mg twice daily) and were typically greater than 2 times the maternal serum levels (see **ADVERSE REACTIONS**).

Nevirapine: No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. In rats, a significant decrease in fetal body weight occurred at doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended human clinical dose. The maternal and developmental no-observable-effect level dosages in rats and rabbits produced systemic exposures approximately equivalent to or approximately 50% higher, respectively, than those seen at the recommended daily human dose, based on AUC. There are no adequate and well-controlled studies in pregnant women. Nevirapine containing products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV infection. It is unclear if pregnancy augments the already increased risk observed in non-pregnant women (see **BOXED WARNING**).

Zidovudine: Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/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/kg/day and rabbits given 500 mg/kg/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/kg/day (very near the oral median lethal dose in rats of 3,683 mg/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 area-under-the-curve (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/kg/day or less. Two rodent transplacental carcinogenicity studies were conducted.

A randomized, double blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV-transmission. Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

Nursing Mothers:

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets.

Lamivudine: A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Lamivudine is also excreted in human 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.

Nevirapine: Nevirapine is excreted in breast milk.

Zidovudine: Zidovudine is excreted in human milk.

Pediatric Use

Adjustment of the dose of lamivudine, nevirapine or zidovudine is not possible with this fixed dose combination. Therefore, Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are not recommended for patients <12 years of age or those who weigh <50 kg.

Geriatric Use

Lamivudine and Zidovudine: Lamivudine and zidovudine are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are not recommended in patients with creatinine clearance ≤ 50 mL/min.

ADVERSE REACTIONS

Adverse events have been reported with lamivudine, nevirapine and zidovudine used as part of antiretroviral combination therapy of HIV infected patients. Adverse events reported with lamivudine, nevirapine and zidovudine may be expected with the use of Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets.

The adverse events reported with lamivudine, nevirapine and zidovudine are presented below.

Lamivudine Plus Zidovudine Administered as Separate Formulations

In four randomized, controlled trials of lamivudine 300 mg per day plus zidovudine 600 mg per day compared with zidovudine 600 mg per day, the following selected clinical and laboratory adverse events were observed (see Tables **5** and **6**).

Table 5: Selected Clinical Adverse Events (≥5% frequency) in Four Controlled Clinical Trials

Adverse Event	Lamivudine 150 mg twice daily plus zidovudine	Zidovudine*
Body as a whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous system		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	13%	18%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

*Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

Pancreatitis was observed in patients (0.3%) who received lamivudine in the controlled clinical trials.

Selected laboratory abnormalities observed during therapy have been summarized in Table 6.

Table 6: Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies and a Clinical Endpoint Study.

Test (Threshold Level)	24- Week Surrogate Endpoint Studies* Lamivudine + Zidovudine	Zidovudine**	Clinical Endpoint Study* Lamivudine + Current Therapy	Placebo + Current Therapy***
Absolute neutrophil count (<750/mm³)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (<50,000/mm³)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

*The median duration on study was 12 months.

** Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

***Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal; ND = Not done.

Observed During Clinical Practice:

In addition to adverse events reported from the clinical trial, the following events have been identified during post-approval use of lamivudine. 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.

Body as a whole: Redistribution/accumulation of body fat (see **PRECAUTIONS**).

Digestive: Stomatitis.

Endocrine and metabolic: Hyperglycemia.

General: 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 exacerbation of hepatitis B, jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure (see **WARNINGS** and **PRECAUTIONS**).

Hypersensitivity: Anaphylaxis, urticaria, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities (see **WARNINGS**) plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction. Allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis, arthralgia.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin and appendages: Alopecia, pruritis, rash, Stevens-Johnson syndrome.

Zidovudine:

Adults: The frequency and severity of adverse events associated with the use of zidovudine are greater in patients with more advanced infection at the time of initiation of therapy. In a zidovudine monotherapy study, the following adverse events were more frequent among patients receiving zidovudine than placebo:

Body as a whole: Asthenia (8.6%*), headache (62.5%), malaise (53.2%)

Gastrointestinal: Anorexia (20.1%), constipation (6.4%*), nausea (51.4%), vomiting (17.2%)

In addition to the adverse events listed above, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.

Selected laboratory abnormalities observed during a clinical study of monotherapy with zidovudine (500 mg/day) in patients with asymptomatic HIV infection are anemia (Hgb<8 g/dL) 1.1%, granulocytopenia (<750 cells/mm³) 1.8%, thrombocytopenia (platelets<50,000/mm³) 0%, ALT [>5 X Upper limit of normal (ULN)] 3.1%, AST (>5 X ULN) 0.9%, alkaline phosphatase (>5 X ULN) 0%.

Observed During Clinical Practice

In addition to adverse events reported from clinical trials, the following events have been identified during use of zidovudine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to zidovudine, or a combination of these factors.

Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain, redistribution/accumulation of body fat.

Cardiovascular: Cardiomyopathy, syncope.

Endocrine: Gynecomastia.

Eye: Macular edema.

Gastrointestinal: Constipation, dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.

General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.

Hemic and Lymphatic: Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.

Hepatobiliary Tract and Pancreas: Hepatitis, hepatomegaly with steatosis, jaundice, lactic acidosis, pancreatitis.

Musculoskeletal: Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor.

Nervous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.

Respiratory: Cough, dyspnea, rhinitis, sinusitis.

Skin: Changes in skin and nail pigmentation, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweat, urticaria.

Special Senses: Amblyopia, hearing loss, photophobia, taste perversion.

Urogenital: Urinary frequency, urinary hesitancy.

Nevirapine:

The most serious adverse reactions associated with nevirapine are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction (see **WARNINGS**).

Adults: The most common clinical toxicity of nevirapine is rash, which can be severe or life threatening (see **WARNINGS**). Rash occurs most frequently within the first 6 weeks of therapy. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. In controlled clinical trials, Grade 1 and 2 rashes were reported in 13.3% of patients receiving nevirapine compared to 5.8% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 1.5% of nevirapine recipients compared to 0.1% of subjects receiving placebo. Women tend to be at higher risk for development of nevirapine-associated rash.

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4.0% (range 0% to 11.0%) of patients who received nevirapine and 1.2% of patients in control groups. Female gender and higher CD4 counts (>250 cells/mm³ in women and >400 cells/mm³ in men) place patients at increased risk of these events (see **WARNINGS**).

Asymptomatic transaminase elevations (AST or ALT > 5 X ULN) were observed in 5.8% (range 0% to 9.2%) of patients who received nevirapine and 5.5% of patients in control groups. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine is associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving nevirapine in placebo-controlled trials are shown in Table below.

Table 7: Percentage of Patients with Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials

	Nevirapine[1] n=1121	Placebo[1] n=1128	Nevirapine[2] n=253	Placebo[2] n=203
Median exposure (weeks)	58	52	28	28
Any adverse event	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Abnormal LFTs	1.2	0.9	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0
Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2.0	0.5
Abdominal pain	0.1	0.4	2.0	0
Myalgia	0.2	0	1.2	2.0

[1]Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm³.

[2]Background therapy included ZDV and ZDV+ddI; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count ≥200 cells/mm³.

Laboratory Abnormalities: Liver function test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls. Asymptomatic elevations in GGT occur frequently but are not a contraindication to continue nevirapine therapy in the absence of elevations in other liver function tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing nevirapine and control regimens.

Table 8: Percentage of Adults Patients with Laboratory Abnormalities

Laboratory Abnormality	Nevirapine[1] n=1121	Placebo[1] n=1128	Nevirapine[2] n=253	Placebo[2] n=203
Blood Chemistry				
SGPT (ALT) >250 U/L	5.3%	4.4%	14.0%	4.0%
SGOT (AST) >250 U/L	3.7	2.5	7.6	1.5
Bilirubin >2.5 mg/dL	1.7	2.2	1.7	1.5
Hematology				
Hemoglobin <8.0 g/dL	3.2	4.1	0	0
Platelets <50,000/mm³	1.3	1.0	0.4	1.5
Neutrophils <750/mm³	13.3	13.5	3.6	1.0

[1] Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm³.

[2] Background therapy included ZDV and ZDV+ddI; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count ≥200 cells/mm³.

Observed During Clinical Practice

In addition to the adverse events identified during clinical trials, the following events have been reported with the use of nevirapine in clinical practice:

Body as a Whole: fever, somnolence, drug withdrawal (see **PRECAUTIONS: Drug Interactions**), redistribution/accumulation of body fat (see **PRECAUTIONS**).

Gastrointestinal: vomiting

Liver and Biliary: jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure

Hematology: anemia, eosinophilia, and neutropenia

Musculoskeletal: arthralgia

Neurologic: paraesthesia

Skin and Appendages: allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities (see **WARNINGS**) plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of nevirapine.

OVERDOSAGE

Lamivudine: There is no known antidote for lamivudine. One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported. One case was a single dose of 7 mg/kg of lamivudine; the second case involved use of 5 mg/kg of lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. 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. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as require.

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. All 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, GZDV, is enhanced.

Nevirapine: There is no known antidote for nevirapine overdosage. Cases of nevirapine overdose at doses ranging from 800 to 1800 mg per day for up to 15 days have been reported. Patients have experienced events including edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting and weight decrease. All events subsided following discontinuation of nevirapine.

DOSAGE AND ADMINISTRATION

Adults:

Lead-in (Initial 14 days of dosing): If fixed dose combination tablets are used during the lead-in phase, the recommended oral dose is one Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablet taken once per day taken followed 12 hours later with a daily oral dose of lamivudine 150 mg and zidovudine 300 mg. The lead-in phase of nevirapine is associated with lower risks of serious rash.

Maintenance: If the initial 14 days of nevirapine is tolerated, the recommended oral dose is one Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablet taken twice daily (at 12 hour intervals).

Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets may be taken without regard to meals.

Pediatrics

Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are not suitable for children ≤12 years and weighing ≤50 kg. For children >12 years and weighing >50 kg dosing is same as for adults.

Geriatrics

Although no specific dosage alterations are recommended, caution should be exercised when Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are administered to geriatric patients (> 65 years of age).

Renal Impairment

In view of the strengths of the individual drug components of this product, Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are not suitable for use in patients with renal impairment (creatinine clearance < 50 ml/min) or for patients on haemodialysis.

Hepatic Impairment

Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are not suitable for patients with hepatic impairment.

Monitoring and Dose Adjustment:

Nevirapine: Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment with nevirapine. The optimal frequency of monitoring during this period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation, and at two weeks post dose escalation. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment.

Nevirapine may cause severe rash or a rash accompanied by constitutional findings. If these symptoms occur, treatment with Nevirapine-containing drug products should be discontinued. Nevirapine can cause hepatitis. If clinical hepatitis occurs, Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets should be discontinued and not restarted after recovery.

For patients who have severe rash or a rash accompanied by constitutional symptoms or patients who have clinical hepatitis, treatment with Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets should be discontinued.

Patients who interrupt dosing with Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets for more than 7 days should restart the recommended 14-day lead-in dosing with once daily Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets followed after 12 hours with a daily dose of lamivudine and zidovudine. Maintenance dosing may resume after 14 days.

Zidovudine: Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia. Dose interruption, dose discontinuation and/or blood transfusion may be warranted in patients who develop significant anemia. In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

If marrow recovery occurs following dose interruption, resumption in therapy may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level and patient tolerance.

For patients experiencing pronounced anemia while receiving chronic coadministration of Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets and some other drugs (e.g., fluconazole, valproic acid), dose interruption of the fixed dose tablets may be considered.

For patients requiring discontinuation of zidovudine treatment due to hematological toxicity (ies), treatment with Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets should be discontinued.

How Supplied

Lamivudine, Zidovudine, Nevirapine Tablets, containing 150 mg lamivudine, 300 mg zidovudine, and 200 mg nevirapine, white, modified capsule shaped, biconvex, film coated tablets, debossed with 'C' on one side and '72' on the other side. They are available as follows:

60 Tablets/Bottle NDC 65862-108-60

Carton of 6 x 10 Unit-dose Tablets NDC 65862-108-10

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Store in a safe place out of the reach of children.

All brands listed are the trademarks of their respective owners and are not trademarks of Aurobindo Pharma Limited.

REFERENCES

1. Scaling up Antiretroviral Therapy in Resource-limited Settings. Guidelines for a Public Health Approach. Published by WHO, June 2002: 52-53, Editors: Hammer S., Gibb D., Mofenson L., Van Beck I., Vella S.
2. http://hivinsite.vesf.edu/insite. Database of Antiretroviral Drug Interactions; All Interactions with Nevirapine (Viramune) (Website developed by the Center for HIV Information (CHI) at the University of California San Francisco (UCSF).

Manufactured for:
Aurobindo Pharma USA, Inc.
2615 route 130 South
Cranbury, NJ 08512

Manufactured by:
Aurobindo Pharma Limited
Hyderabad-500 072, India

Issued: June 2006

P1500590

doctor prescribes it. The usual dose is 1 tablet two times a day after the first 14 days of starting HIV medicines. For the first 14 days the dose is one daily tablet followed 12 hours later with lamivudine and zidovudine tablets that do not contain nevirapine.

- You can take lamivudine, zidovudine and nevirapine tablets with or without food.
- Do not miss a dose of lamivudine, zidovudine and nevirapine tablets, because this could make the virus harder to treat. If you forget to take lamivudine, zidovudine and nevirapine tablets, take the missed dose right away. If it is almost time for your next dose, do not take the missed dose. Instead, follow your regular dosing schedule by taking the next dose at its regular time.
- Do not let your lamivudine, zidovudine and nevirapine tablets run out.
- If you stop taking lamivudine, zidovudine and nevirapine tablets for more than 7 days, ask your doctor before you start taking them again.
- If you suspect that you have taken too many lamivudine, zidovudine and nevirapine tablets, contact your local poison control center or emergency room right away.

Can I take other medicines with lamivudine, zidovudine and nevirapine tablets?

- Lamivudine, zidovudine and nevirapine tablets may change the effect of other medicines, and other medicines can change the effect of lamivudine, zidovudine and nevirapine tablets. Tell your doctors and pharmacists about **all** medicines you take, including non-prescription medicines, vitamins and herbal supplements.
- Do **not** take Nizoral® (ketoconazole) or Rifadin®/Rifamate®/Rifater® (rifampin) with lamivudine, zidovudine and nevirapine tablets.
- Tell your doctor if you take Biaxin® (clarithromycin), Diflucan®(fluconazole), doxorubicin, methadone, Mycobutin®(rifabutin) or ribavirin. Lamivudine, zidovudine and nevirapine tablets may not be right for you, or you may need careful monitoring.
- It is recommended that you do not take products containing St. John's wort, which can reduce the amount of nevirapine in your body.
- If you take birth control pills, you should not rely on them to prevent pregnancy. They may not work if you take lamivudine, zidovudine and nevirapine tablets. Talk with your doctor about other types of birth control that you can use.

What should I avoid while taking lamivudine, zidovudine and nevirapine tablets?

- Do not take Epivir (lavmivudine, 3TC), Retrovir (Zidovudine, AZT, ZDV, azidothymidine), Combivir (lamivudine and zidovudine), Epzicom (abacavir sulfate and lamivudine), Trizivir (abacavir sulfate, lamivudine, and zidovudine) or Viramune (nevirapine) while taking lamivudine, zidovudine and nevirapine tablets. Some of these medicines are already in lamivudine, zidovudine and nevirapine tablets.
- Do not take Zerit (stavudine, d4T) or HIVID (zalcitabine, ddC) while taking lamivudine, zidovudine and nevirapine tablets.
- Avoid doing things that can spread HIV infection, as lamivudine, zidovudine and nevirapine tablets do not stop you from passing HIV infection to others.
- Do not share needles, other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- Do not breastfeed. Lamivudine, zidovudine and nevirapine tablets can be passed to babies in breast milk and could harm the baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.

What are the possible side effects of lamivudine, zidovudine and nevirapine tablets?

- **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.** (See "What is the most important information I should know about lamivudine, zidovudine and nevirapine tablets?" at the beginning of this Medication Guide.)
- **Worsening of HBV infection.** (See "What is the most important information I should know about lamivudine, zidovudine and nevirapine tablets?" at the beginning of this Medication Guide.)
- **Hematologic toxicity including neutropenia and severe anemia.** (See "What is the most important information I should know about lamivudine, zidovudine and nevirapine tablets?" at the beginning of this Medication Guide.)
- **Serious liver damage and skin reactions that can cause death.** (See "What is the most important information I should know about lamivudine, zidovudine and nevirapine tablets?" at the beginning of this Medication Guide.)
- **Changes in body fat.** These changes have happened in patients taking antiretroviral medicines like lamivudine, zidovudine and nevirapine tablets. The changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Other common side effects of lamivudine, zidovudine and nevirapine tablets include nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain, depression/anxiety, and myalgia. This list of side effects is not complete. Ask your doctor or pharmacist for more information.

How do I store lamivudine, zidovudine and nevirapine tablets?

Store lamivudine, zidovudine and nevirapine tablets at room temperature, between 59° to 89°F (15° to 30°C).

Throw away lamivudine, zidovudine and nevirapine tablets that are no longer needed or out-of-date.

Keep lamivudine, zidovudine and nevirapine tablets and all medicines out of the reach of children.

General information for safe and effective use of lamivudine, zidovudine and nevirapine tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use lamivudine, zidovudine and nevirapine tablets for a condition for which it was not prescribed. Do not give lamivudine, zidovudine and nevirapine tablets to other people, even if they have the same condition you have. It may harm them.

This Medication Guide summarizes the most important information about lamivudine, zidovudine and nevirapine tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about lamivudine, zidovudine and nevirapine tablets that is written for health professionals.

What are the ingredients in lamivudine, zidovudine and nevirapine tablets?

Active ingredients: lamivudine, zidovudine and nevirapine.

Inactive ingredients: Each film coated lamivudine, zidovudine and nevirapine tablets contains the inactive ingredients colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, sodium starch glycolate and titanium dioxide.

All brands listed are the trademarks of their respective owners and are not trademarks of Aurobindo Pharma Limited.

This Medication Guide has been approved by the US Food and Drug Administration

Manufactured for:
Aurobindo Pharma USA, Inc.
2615 route 130 South
Cranbury, NJ 08512

Manufactured by:
Aurobindo Pharma Limited
Hyderabad-500 072, India

Issued: June 2006