5041-2009-05
Lamivudine/Zidovudine Tablets, 150/300 mg Co-packaged with Nevirapine Tablets USP, 200 mg
Rx Only
Rev.01
2006761-00

Lamivudine/Zidovudine Tablets, 150 mg/300 mg Co-packaged with Nevirapine Tablets, 200 mg

PRESCRIBING INFORMATION

Rx Only

WARNINGS

ZIDOVUDINE, ONE OF THE TWO ACTIVE INGREDIENTS IN LAMIVUDINE/ZIDOVUDINE TABLETS, HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS 1 (HIV-1) DISEASE (SEE WARNINGS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY (SEE WARNINGS).

LACTIC ACIDOSIS AND 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. SUSPEND TREATMENT IF CLINICAL OR LABORATORY FINDINGS SUGGESTIVE OF LACTIC ACIDOSIS OR PRONOUNCED HEPATOTOXICITY OCCUR (SEE WARNINGS).

ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV-1 AND HAVE DISCONTINUED LAMIVUDINE, WHICH IS ONE COMPONENT OF LAMIVUDINE/ZIDOVUDINE TABLETS. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVUDINE /ZIDOVUDINE TABLETS AND ARE CO-INFECTED WITH HIV-1 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+ CELL COUNTS AT INITIATION OF THERAPY PLACE PATIENTS AT INCREASED RISK; WOMEN WITH CD4+ CELL COUNTS > 250 CELLS/MM3, INCLUDING PREGNANT WOMEN RECEIVING NEVIRAPINE IN COMBINATION WITH OTHER ANTIRETROVIRALS FOR THE TREATMENT OF HIV-1 INFECTION, ARE AT THE GREATEST RISK. HOWEVER, HEPATOTOXICITY ASSOCIATED WITH NEVIRAPINE USE CAN OCCUR IN BOTH GENDERS, ALL CD4+ CELL 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 STAVUDINE, LAMIVUDINE AND NEVIRAPINE 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 AND ZIDOVUDINE TABLETS CO-PACKAGED WITH NEVIRAPINE TABLETS AND SEEK MEDICAL EVALUATION IMMEDIATELY. TRANSAMINASE LEVELS SHOULD BE CHECKED IMMEDIATELY FOR ALL PATIENTS WHO DEVELOP A RASH IN THE FIRST 18 WEEKS OF TREATMENT. THE 14-DAY LEAD-IN PERIOD WITH NEVIRAPINE DAILY DOSING HAS BEEN OBSERVED TO DECREASE THE INCIDENCE OF RASH AND MUST BE FOLLOWED (SEE WARNINGS AND PRECAUTIONS).

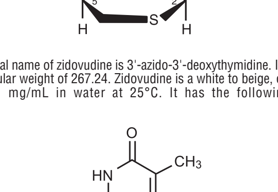
PATIENTS MUST BE MONITORED INTENSIVELY DURING THE FIRST 18 WEEKS OF THERAPY WITH NEVIRAPINE CONTAINING DRUG PRODUCTS TO DETECT POTENTIALLY LIFE-THREATENING HEPATOTOXICITY OR SKIN REACTIONS. EXTRA VIGILANCE IS WARRANTED DURING THE FIRST 6 WEEKS OF THERAPY, WHICH IS THE PERIOD OF GREATEST RISK OF THESE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

DESCRIPTION

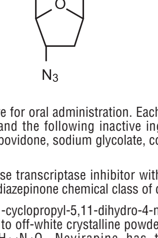
Lamivudine/Zidovudine Tablets: Lamivudine/Zidovudine Tablets are combination tablets containing lamivudine and zidovudine. Lamivudine and zidovudine (azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against HIV.

Lamivudine/Zidovudine Tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate and opadry white (hypromellose, polyethylene glycol, polysorbate 80 and titanium dioxide).

Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3- oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26. Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C. It has the following structural formula:



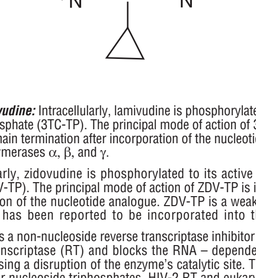
Zidovudine: The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of $C_{10}H_{13}N_5O_4$ and a molecular weight of 267.24. Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C. It has the following structural formula:



Nevirapine: Nevirapine tablets are for oral administration. Each nevirapine tablet contains 200 mg of nevirapine as the active ingredient and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, corn starch, povidone, sodium glycolate, colloidal silicon dioxide and magnesium stearate.

Nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. Nevirapine is structurally a member of the dipyridodiazepinone chemical class of compounds.

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:



MICROBIOLOGY

Mechanism of Action: ***Lamivudine:*** Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.3TC-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Zidovudine: Intracellularly, zidovudine is phosphorylated to its active 5'- triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and 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. Nevirapine 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, and γ, or δ) are not inhibited by nevirapine.

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

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values (50% effective concentrations) were in the range of 0.003 to 15 µM (1 µM = 0.23 mcg/mL). HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.429 µM (range: 0.200 to 2.007 µM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 µM (1.37 to 3.68 µM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 µM, and against HIV-2 isolates from 0.003 to 0.120 µM in peripheral blood mononuclear cells. Ribavirin (50 µM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

Zidovudine: The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The EC_{50} and EC_{90} values for zidovudine were 0.01 to 0.49 µM (1 µM = 0.27 mcg/mL) and 0.1 to 9 µM, respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.011 µM (range: 0.005 to 0.110 µM) from Virco (n = 92 baseline samples from COLA40263) and 0.0017 µM (0.006 to 0.0340 µM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 µM, and against HIV-2 isolates from 0.00049 to 0.004 µM. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, and lamivudine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Nevirapine: The cell culture antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. In recent studies using human cord blood lymphocytes and human embryonic kidney 293 cells, EC_{50} values (50% inhibitory concentration) ranged from 14 to 302 nM against laboratory and clinical isolates of HIV-1. Nevirapine exhibited antiviral activity in cell culture against group M HIV-1 isolates from clades A, B, C, D, F, G, and H, and circulating recombinant forms (CRF) CRF01_AE, CRF02_AG and CRF12_BF (median EC_{50} value of 63 nM). Nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates or HIV-2 isolates. Nevirapine in combination with efavirenz exhibited strong antagonistic anti-HIV-1 activity in cell culture and was to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor enfuvirtide. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin in cell culture.

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 amino acid substitutions 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 amino acid substitutions, the most essential of which may be G333E. The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

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

Zidovudine: HIV isolates with reduced susceptibility to zidovudine have been selected in cell culture and were also recovered from patients treated with zidovudine. Genotypic analyses of the isolates selected in cell culture and recovered from zidovudine- treated patients showed substitutions in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of amino acid substitutions.

Nevirapine: HIV-1 isolates with reduced susceptibility (100- to 250-fold) to nevirapine emerge in cell culture. Genotypic analysis showed mutations in the HIV-1 RT gene encoding Y181C and/or V106A substitutions depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance in cell culture was not altered when selection included nevirapine in combination with several other NNRTIs. 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 substitutions: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve patients receiving either nevirapine (n=24) or nevirapine and ZDV (n=14) 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 cell culture. One or more of the RT mutations resulting in amino acid substitutions 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 cell culture compared to baseline, and had one or more of the nevirapine associated RT resistance mutations. Nineteen of these 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 substitutions: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

Cross-Resistance: Cross-resistance has been observed among NRTIs.

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 substitution at codon 184, which confers resistance to lamivudine. Cross-resistance to abacavir, didanosine, and tenofovir has been observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients treated with zidovudine plus didanosine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below).

Lamivudine: See Lamivudine Plus Zidovudine (above).

Zidovudine: In a study of 167 HIV-1-infected patients, isolates (n = 2) with multi-drug resistance to didanosine, lamivudine, stavudine, and zidovudine were recovered from patients treated for ≥1 year with zidovudine plus didanosine. The pattern of resistance- associated amino acid substitutions with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M substitutions being most commonly associated with multi-drug resistance. The substitution at codon 151 in combination with substitutions at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, and zidovudine. Thymidine analogue mutations (TAMs) are selected by zidovudine and confer cross- resistance to abacavir, didanosine, stavudine, and tenofovir.

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

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults:

Lamivudine /Zidovudines: The rate and extent of absorption of Lamivudine/ Zidovudine from the combination tablets were similar to that from Combivir® tablets containing lamivudine 150 mg and zidovudine 300 mg when administered to healthy volunteers in the fasted and fed state.

Nevirapine: The rate and extent of absorption of Nevirapine from the co-packaged tablets were similar to that from Viramune® 200 mg tablets when administered to healthy volunteers in the fasted and fed state.

Lamivudine: The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 1. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

Zidovudine: The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is 3'-azido-3'-deoxy-5'-O-β-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% of the dose following oral administration, respectively. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the zidovudine AUC.

Table 1. Pharmacokinetic Parameters* for Lamivudine and Zidovudine in Adults

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

*Data presented as mean ± standard deviation except where noted.
† Median [range].
‡ Children.
§ Adults.
‖ Approximate range.

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 12 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) were 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 µ/mL (17 ± 7 µM), (n = 242) were attained at 400 mg/day.

Distribution: Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (Vdss) of nevirapine is 1.21 ± 0.09 L/kg, 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 to 10 µ/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 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 CYP3A and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion study in eight 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 3A and 2B6. Nevirapine induces CYP3A and CYP2B6 by approximately 20 to 25%, as indicated by erythromycin breath test results and urine metabolites. Autoinduction of CYP3A 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 to 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 to 30 hours following multiple dosing with 200 to 400 mg/day.

Effect of Food on Absorption of Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets: The effect of food on the rate and extent of absorption of Lamivudine/Zidovudine Tablets, 150mg/300mg Co-packaged with Nevirapine Tablets, 200mg has been evaluate in a clinical study. Therefore, Lamivudine and /Zidovudine Tablets, 150mg/300mg Co-packaged with Nevirapine Tablets, 200mg can be administered with or without food.

Special Populations:

Impaired Renal Function: Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets: Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets are not recommended for patients with impaired renal function or for patients on hemodialysis because Lamivudine/Zidovudine Tablets require dose adjustment in the presence of reduced renal function (creatinine clearance <50 mL/min) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Impaired Hepatic Function: Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets: Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets are not recommended for patients with impaired hepatic function because a reduction in the daily dose of zidovudine, one component of the fixed-dose combination of Lamivudine/Zidovudine Tablets, may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis.

Pregnancy: See PRECAUTIONS: Pregnancy.

Zidovudine: Zidovudine pharmacokinetics has been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine was similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential for interaction has been identified (see CLINICAL PHARMACOLOGY: Drug Interactions).

Nursing Mothers: See PRECAUTIONS: Nursing Mothers.

Lamivudine and Zidovudine: Although no studies of Lamivudine/Zidovudine excretion in breast milk have been performed, lactation studies performed with lamivudine and zidovudine show that both drugs are excreted in human breast milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine. In another study, after administration of a single dose of 200 mg zidovudine to 13 HIV-1-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Pediatric Patients: Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets: Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets should not be administered to pediatric patients weighing less than 30 kg, because this co-packaged product cannot be adjusted for this patient population.

Geriatric Patients: The pharmacokinetics of lamivudine and zidovudine have not been studied in patients over 65 years of age.

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

Gender: Lamivudine/Zidovudine Tablets: A pharmacokinetic study in healthy male (n =12) and female (n = 12) subjects showed no gender differences in zidovudine exposure (AUC∞) or lamivudine AUC∞ normalized for body weight.

Nevirapine: In the multinational 2NN study a population pharmacokinetic substudy of 1077 patients was performed that included 391 females. Female patients showed a 13.8% lower clearance of nevirapine than did men. Since neither body weight nor Body Mass Index (BMI) had an influence on the clearance of nevirapine, the effect of gender cannot solely be explained by body size.

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

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

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 steady-state C_{min} = 4.7 µ/mL Black, 3.8 µ/mL Hispanic, 4.3 µ/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: Drug Interactions.

No drug interaction studies have been conducted with Lamivudine/Zidovudine Tablets Co- packaged with Nevirapine Tablets.

Lamivudine/Zidovudine Tablets: No drug interaction studies have been conducted using Lamivudine/Zidovudine Tablets. However, Table 2 presents drug interaction information for the individual components of Lamivudine/Zidovudine Tablets.

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).

Table 2. Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC*
Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

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

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

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

Nevirapine: Nevirapine induces hepatic cytochrome P450 metabolic isoenzymes 3A and 2B6. Co-administration of nevirapine 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 3A 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 (CYP3A). The estimated Ki for the inhibition of CYP3A was 270 mcmol, a concentration that is unlikely to be achieved in patients as the therapeutic range is <25 mcmol. Therefore, nevirapine may have minimal inhibitory effect on other substrates of CYP3A.

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.

Table 3 (see 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 3 Drug Interactions: 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)		
Antiretrovirals				AUC	C_{max}	C_{min}
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 - ↓14)	↓12 (↓23 - ↑1)	↓32 (↓35 -↓19)
Indinavir[a]	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 - ↓22)	↓15 (↓24 - ↓4)	↓44 (↓53 - ↓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]	↓22 (↓44 - ↑9)	↓14 (↓36 - ↑16)	↓55 (↓75 - ↓19)
Lopinavir[a]	400/100 mg BID (lopinavir/ ritonavir)	200 mg QD x 14 days; 200 mg BID > 1 year	22, 19[c]	↓27 (↓47 - ↓2)	↓19 (↓38 - ↑5)	↓51 (↓72 - ↓26)
Nelfinavir[a]	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	⇔	⇔	↓32 (↓50 - ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 - ↓53)	↓59 (↓68 - ↓48)	↓66 (↓74 - ↓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 - ↓11)	↓32 (↓44 - ↓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 - ↓4)	↓30 (↓51 - ↑14)	§
Other Medications				AUC	C_{max}	C_{min}
Clarithromycin[a]	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓31 (↓38 - ↓24)	↓23 (↓31 - ↓14)	↓57 (↓70 - ↓36)
Metabolite 14-OH -clarithromycin				↑42 (↑16 - ↑73)	↑47 (↑21 - ↑80)	⇔
Ethinyl estradiol[a] and	0.035 mg (as Ortho-Novum® 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 - ↓3)	⇔	§
Norethindrone[a]	1 mg (as Ortho-Novum® 1/35)			↓19 (↓30 - ↓7)	↓16 (↓27 - ↓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 - ↓60)	↓44 (↓58 - ↓27)	§
Methadone[a]	Individual Patient Dosing	200 mg QD x 14 days; 200 mg BID ≥ 7days	9	In a controlled pharmacokinetic study with 9 patients receiving chronic methadone to whom steady state nevirapine therapy was added, the clearance of methadone was increased by 3-fold resulting in symptoms of withdrawal, requiring dose adjustments in 10 mg segments, in 7 of the 9 patients. Methadone did not have any effect on nevirapine clearance.		
Rifabutin[a]	150 or 300 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↑17 (↓2 - ↑40)	↑28 (↑9 - ↑51)	⇔
Metabolite 25-O-desacetyl-rifabutin				↑24 (↓16 - ↑84)	↑29 (↓2 - ↑68)	↑22 (↓14 - ↑74)
Rifampin[a]	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑11 (↓4 - ↑28)	⇔	§

§ = C_{min} below detectable level of the assay
↑ = Increase, ↓ = Decrease, ⇔ = No Effect
[a] For information regarding clinical recommendations see Drug Interactions
[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 [*see* **PRECAUTIONS: Drug Interactions, Table 6**). The effects of other drugs listed in Table 3 on nevirapine pharmacokinetics were not significant. No significant interaction was observed when tipranavir was co-administered with low dose ritonavir and nevirapine.

INDICATIONS AND USAGE

Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets are indicated alone or in combination with other antiretrovirals for the treatment of HIV-1 infection.

Additional important information regarding the use of nevirapine (a component of Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets) for the treatment of HIV-1 infection:

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, nevirapine should not be initiated in adult females with CD4+ cell counts greater than 250 cells/mm³ or in adult males with CD4+ cell counts greater than 400 cells/mm3 unless the benefit outweighs the risk (see WARNINGS).
- A 14-day lead-in period with nevirapine 200 mg once daily dosing has been demonstrated to reduce the frequency of rash (see WARNINGS and DOSAGE AND ADMINISTRATION).
- If rash persists beyond the 14 day lead-in period, do not dose escalate to 200 mg twice daily. The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point an alternative drug regimen should be sought.

Description of Clinical Studies: ***Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets:*** There have been no clinical trials conducted with Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets. See CLINICAL PHARMACOLOGY for information about pharmacokinetic comparability.

Lamivudine Plus Zidovudine: The NUCB3007 (CAESAR) study was conducted using lamivudine 150-mg Tablets (150 mg twice daily) and zidovudine 100-mg Capsules (2 x 100 mg 3 times daily). CAESAR was a multi-center, double-blind, placebo-controlled study comparing continued current therapy [zidovudine alone (62% of patients) or zidovudine with didanosine or zalcitabine (38% of patients)] to the addition of lamivudine or lamivudine plus an investigational non-nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1,816 HIV-infected adults with 25 to 250 (median 122) CD4+ cells/mm³ at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on study was 12 months. Results are summarized in Table 4.

Table 4. Number of Patients (%) With At Least 1 HIV Disease-Progression Event or Death

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

* An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

Nevirapine: Trial BI 1090, was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1-infected patients with <200 CD4+ cells/mm³ at screening. Initiated in 1995, BI 1090 compared treatment with nevirapine + lamivudine + background therapy versus lamivudine + background therapy in NNRTI naïve patients. Treatment doses were nevirapine, 200 mg daily for two weeks followed by 200 mg twice daily or placebo, and lamivudine 150 mg twice daily. Other antiretroviral agents were given at approved doses. Initial background therapy (in addition to lamivudine) was one NRTI in 1309 patients (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%). The patients (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV infection, with a median baseline CD4+ cell count of 96 cells/mm³ and a baseline HIV RNA of 4.58 $\log_{10}$ copies/mL (38,291 copies/mL). Prior to entering the trial, 45% had previously experienced an AIDS-defining clinical event. Eighty-nine percent had antiretroviral treatment prior to entering the trial. BI 1090 was originally designed as a clinical endpoint study. Prior to unblinding the trial, the primary endpoint was changed to proportion of patients with HIV RNA <50 copies/mL and not previously failed at 48 weeks. Treatment response and outcomes are shown in Table 5.

Table 5. BI 1090 Outcomes through 48 weeks

Outcome	Nevirapine (N=1121) %	Placebo (N=1128) %
Responders at 48 weeks: HIV RNA <50 copies/mL	18.0	1.6
Treatment Failure	82.0	98.4
Never suppressed viral load	44.6	66.4
Virologic failure after response	7.2	4.3
CDC category C event or death	9.6	11.2
Added antiretroviral therapy[1] while <50 copies/mL	5.0	0.9
Discontinued trial therapy due to AE	7.0	5.9
Discontinued trial <48 weeks[2]	8.5	9.8

[1] including change to open-label NVP
[2] includes withdrawal of consent, lost to follow-up, non-compliance with protocol, other administrative reasons

The change from baseline in CD4+ cell count through one year of therapy was significantly greater for the nevirapine group compared to the placebo group for the overall study population (64 cells/mm³ vs 22 cells/mm³, respectively), as well as for patients who entered the trial as treatment naive or having received only ZDV (85 cells/mm³ vs 25 cells/mm³, respectively).

At two years into the study, 16% of subjects on nevirapine had experienced class C CDC events as compared to 21% of subjects on the control arm.

Trial BI 1046 (INCAS) was a double-blind, placebo-controlled, randomized, three arm trial with 151 HIV-1 infected patients with CD4+ cell counts of 200-600 cells/mm³ at baseline. BI 1046 compared treatment with nevirapine + zidovudine + didanosine to nevirapine + zidovudine and zidovudine + didanosine. Treatment doses were nevirapine at 200 mg daily for two weeks followed by 200 mg twice daily or placebo, zidovudine at 200 mg three times daily, and didanosine at 125 or 200 mg twice daily (depending on body weight). The patients had mean baseline HIV RNA of 4.41 log10 copies/mL (25,704 copies/mL) and mean baseline CD4+ cell count of 376 cells/mm³. The primary endpoint was the proportion of patients with HIV-RNA < 400 copies/mL and not previously failed at 48 weeks. The virologic responder rates at 48 weeks were 45% for patients treated with nevirapine +zidovudine+didanosine, 19% for patients treated with zidovudine+didanosine, and 0% for patients treated with nevirapine +zidovudine.

CD4+ cell counts in the nevirapine +ZDV+ddI group increased above baseline by a mean of 139 cells/mm³ at one year, significantly greater than the increase of 87 cells/mm³ in the ZDV+ddI patients. The nevirapine + ZDV group mean decreased by 6 cells/mm³ below baseline.

CONTRAINDICATIONS

Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product.

WARNINGS

Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine 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 Tablets Co-packaged with Nevirapine Tablets should be consulted before combination therapy with Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets is initiated.

Lamivudine/Zidovudine:

Hemotologic Toxicity/Bone Marrow Suppression: Zidovudine, a component of Lamivudine/Zidovudine, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease. Lamivudine/Zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count less than 1,000 cells/mm³ or hemoglobin less than 9.5 g/dL (see ADVERSE REACTIONS).

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

Lactic Acidosis/Hepatomegaly With Steatosis: Lactic acidosis and 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. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering Lamivudine/Zidovudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Lamivudine/Zidovudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-1-infected patients treated with lamivudine for chronic HBV, 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-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

Use With Interferon- and Ribavirin-Based Regimens: *In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine or zidovudine in HIV-1/HCV co- infected patients (see CLINICAL PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and Lamivudine/Zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of Lamivudine/Zidovudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh greater than 6) (see the complete prescribing information for interferon and ribavirin). Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Co-administration of ribavirin and zidovudine is not advised.

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 enzyme 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 or rash (see **DOSAGE AND ADMINSTRATION**).

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. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use. 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 of 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/Zidovudine Tablets Co-packaged with Nevirapine Tablets and seek medical evaluation immediately (see PRECAUTIONS). Do not restart Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine 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 Tablets Co-packaged with Nevirapine Tablets.

Therapy with nevirapine must be initiated with a 14-day lead-in period of 200 mg/day (150mg/m2/day in pediatric patients), which has been shown to reduce the frequency of rash. Nevirapine should be discontinued if a patient experiences severe rash or any rash accompanied by constitutional findings. A patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200mg/day (150mg/m/day in pediatric patients) should not have their nevirapine dose increased until the rash has resolved. The total duration of the once daily lead-in dosing period should not exceed 28 days at which point an alternative regimen should be sough (see DOSAGE AND ADMINISTRATION). 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.

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 %) 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. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use. Patients with signs or symptoms of hepatitis must be advised to discontinue Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets and immediately seek medical evaluation, which should include liver enzyme tests.

Transaminases should be checked immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Transaminases should also be checked 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 transaminases 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 Tablets Co-packaged with Nevirapine Tablets should be permanently discontinued. Do not restart Lamivudine/Zidovudine Tablets Co- packaged with Nevirapine 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+ cell 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+ cell counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4+ cell counts >250 cells/mm³ had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4+ cell counts <250 cells/mm³ (11 % versus 0.9 %). An increased risk was observed in men with CD4+ cell counts >400 cells/mm³ (6.3 % versus 1.2 % for men with CD4+ cell counts >400 cells/mm 3). However, all patients, regardless of gender, CD4+ cell count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4+ cell counts. Co-infection with hepatitis B or C and/or increased transaminase elevations 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.

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.

Increased nevirapine trough concentrations have been observed in some patients with hepatic fibrosis or cirrhosis. Therefore, patients with either hepatic fibrosis or cirrhosis should be monitored carefully for evidence of drug induced toxicity. Nevirapine should not be administered to patients with moderate or severe (Child Pugh Class B or C, respectively) hepatic impairment (see **CONTRAINDICATIONS, CLINICAL PHARMACOLOGY: Special Populations**).

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, nevirapine should not be administered to patients with severe hepatic impairment. (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations: Hepatic Impairment; PRECAUTIONS; General**).

Resistance: Nevirapine must not be used as a single agent to treat HIV-1 infection or added on as a sole agent to a failing regimen. Resistant virus emerges rapidly when nevirapine is administered as monotherapy.

⬆ DETACH BEFORE DISPENSING

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

MEDICATION GUIDE

Lamivudine/Zidovudine Tablets, 150 mg/300 mg Co-packaged with Nevirapine Tablets, 200 mg

Rx Only

Generic name: Lamivudine/zidovudine (lah MIH vue deen and zye DOE vue deen) tablets co-packaged with nevirapine (na VAIR a peen) tablets.

Read this Medication Guide before you start taking Lamivudine/Zidovudine Tablets Co- packaged with 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 discuss 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 Tablets Co-packaged with 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 Tablets Co-packaged with Nevirapine Tablets?

Patients taking nevirapine (one of the components of Lamivudine/Zidovudine Tablets Co-packaged with 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.

Take Lamivudine/Zidovudine Tablets and Nevirapine Tablets exactly as instructed. Do not take more than the doctor told you to. Check the label carefully for how much to take and how often to take each medicine.

Your doctor will recommend that you take Lamivudine/Zidovudine Tablets with Nevirapine Tablets twice a day only if you have tolerated a two week "lead-in" period in which you received pills containing nevirapine 200 mg once daily (along with pills containing lamivudine and zidovudine taken twice daily).

Patients taking Lamivudine/Zidovudine Tablets may deveop:

Lactic Acidosis

Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets can cause a condition called lactic acidosis, together with an enlarged liver. Symptoms of lactic acidosis may include:

- feeling very weak and tired;
- nausea, vomiting, or unusual or unexpected stomach discomfort;
- shortness of breath;
- weakness in arms and legs.

If you notice these symptoms or if your medical condition suddenly changes, stop taking Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital.

This rare, but serious side effect occurs more often in women (including pregnant women), overweight patients, and those who have been taking nucleoside medicines for a very long time. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

Worsening of hepatitis B virus (HBV) infection

Patients with HBV infection, who take Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets and then stop it, 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 Tablets Co-packaged with Nevirapine Tablets. You may need to take anti-HBV medications.

Use with interferon- and ribavirin-based regimens

Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C who are taking anti-HIV medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets as well as interferon with or without ribavirin and you experience side effects, be sure to tell your doctor.

Hematologic Toxicity

Lamivudine/Zidovudine Tablets have been associated with hematologic toxicity including neutropenia and/or anemia, particularly in patients with advanced HIV disease. Serious blood problems including low levels of red and/or white blood cells have occurred with the use of zidovudine. Contact your doctor immediately if you develop unusual fatigue, pale skin, sore throat, fever, or chills which may be signs of blood problems.

Prolonged use of lamivudine/zidovudine tablets has been associated with symptomatic myopathy.

Patients taking the co-packaged Nevirapine Tablets may develop:

Liver Reactions

Any patient can experience liver problems while taking nevirapine. However, women and patients who have higher CD4 counts when they begin nevirapine 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 nevirapine 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 nevirapine with abnormal liver function tests and patients with hepatitis B or C have a greater chance of developing further increases in liver tests after starting nevirapine 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 nevirapine and call your doctor right away:

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

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 nevirapine.

Skin Reactions

Skin rash is the most common side effect of nevirapine. 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 nevirapine and call your doctor right away:**

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

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

These are not all the side effects of lamivudine, zidovudine, and nevirapine. See the section **"What are the possible side effects of Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets?"** for more information. Tell your doctor if you have any side effects from nevirapine.

What is lamivudine, zidovudine, and nevirapine (the components of Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets)?

Lamivudine/Zidovudine Tablets with Nevirapine Tablets are antiviral medications. They are medicines used to treat Human Immunodeficiency Virus (HIV), the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

They are in a category of HIV medicines called reverse transcriptase inhibitors. All three medicines work by lowering the amount of HIV in the blood ("viral load"). You must take nevirapine with other anti-HIV medicines. When taken with other anti-HIV medicines, Lamivudine/Zidovudine Tablets with Nevirapine Tablets can reduce viral load and increase the number of CD4 cells ("T cells"). CD4 cells are a type of immune helper cell in the blood. Lamivudine/Zidovudine Tablets with Nevirapine Tablets may not have these effects in every patient.

Lamivudine/Zidovudine Tablets with Nevirapine Tablets do not cure HIV or AIDS, and it is not known if they will help you live longer with HIV.

People taking Lamivudine/Zidovudine Tablets with Nevirapine Tablets may still get infections common in people with HIV (opportunistic infections). Therefore, it is very important that you stay under the care of your doctor.

Lamivudine and zidovudine may also be used for purposes other than those listed in this medication guide.

Who should not take Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets?

- Do not take if you are allergic to lamivudine, zidovudine or nevirapine or any of its ingredients. Your doctor or pharmacist can tell you about the inactive ingredients.
- Do not restart the medication after you recover from side effects of these medications such as serious blood problems, lactic acidosis, serious liver or skin reactions that happened when you took these medications without the advice of your doctor.
- Do not take these medications if you take certain medicines. (See "Can I take other **medicines with Lamivudine/Zidovudine Tablets with Nevirapine Tablets?" for a list of medicines.)**
- Do not take these medications if you are not infected with HIV.

What should I tell my doctor before taking Lamivudine/Zidovudine Tablets with Nevirapine Tablets?

Before starting Lamivudine/Zidovudine Tablets with Nevirapine Tablets, tell your doctor about all of your medical conditions, including if you:

- have problems with your liver or have had hepatitis
- have kidney disease or are undergoing dialysis
- have skin conditions, such as a rash
- are pregnant, planning to become pregnant, or are breast feeding
- have bone marrow suppression
- weigh less than 66 pounds (30 kg)

How should I take Lamivudine/Zidovudine Tablets with Nevirapine Tablets?

Take the medications in this co-package exactly as directed by your doctor. If you do not understand these directions, ask your pharmacist, nurse, or doctor to explain them to you.

Adults and Children/Adolescents weighing more than or equal to 30 kg

The choice of new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential for cross 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 (see **CLINICAL PHARMACOLOGY**).

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 St. John's wort with non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine 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.

Important Differences Among Lamivudine-, Zidovudine-, Nevirapine-, and/or Emtricitabine-Containing Products:

Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets contain a higher dose of the same active ingredient (lamivudine) than in EPIVIR-HBV tablets and oral solution. EPIVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients co- infected with HIV-1 and HBV. **Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets** should not be administered concomitantly with other lamivudine-, zidovudine- or nevirapine-containing products including EPIVIR, EPIVIR-HBV, COMBIVIR, TRIZIVIR, EPZICOM, RETROVIR, VIRAMUNE or emtricitabine- containing products, including ATRIPLA, EMTRIVA, or TRUVADA.

PRECAUTIONS

Lamivudine/Zidovudine:

Patients With HIV-1 and Hepatitis B Virus Co-infection: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV-1 and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see EPIVIR-HBV package insert for additional information).

Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. Posttreatment exacerbations of hepatitis have also been reported (see WARNINGS).

Lamivudine/Zidovudine with Nevirapine:

Patients With Impaired Renal Function: Patients with creatinine clearance <50 mL/min or patients on hemodialysis should not receive Lamivudine/Zidovudine Tablets Co- packaged with Nevirapine Tablets.

Patients With Impaired Hepatic Function: Lamivudine/Zidovudine Tablets Co- packaged with Nevirapine Tablets are not recommended for patients with impaired hepatic function.

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 jiroveci* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

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

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 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**).

Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known **(see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations: Renal Impairment; DOSAGE AND ADMINISTRATION, Dosage Adjustment).**

The duration of clinical benefit from antiretroviral therapy may be limited. Patients receiving nevirapine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV-1 diseases.

When administering nevirapine as part of an antiretroviral regiment, the complete product information for each therapeutic component should be consulted before initiation of treatment.

Information for Patients:

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

Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets: Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets are for oral ingestion only.

Patients should be informed that Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets are not a cure for HIV-1 infection and that they may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should be advised that the use of Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets has not been shown to reduce the risk of transmission of HIV-1 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.

Patients should be informed to take Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets every day as prescribed. Patients should not alter the dose without consulting their doctor. 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.

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 that the long-term effects of lamivudine are unknown at this time. Patients should be advised to discuss any changes in regimen with their physician.

Patients should be advised that Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets contain a higher dose of the same active ingredient (lamivudine) as EPIVIR-HBV tablets. If a decision is made to include lamivudine in the HIV-1 treatment regimen of a patient dually infected with HIV-1 and HBV, the dosage of lamivudine in Lamivudine /Zidovudine Tablets Co-packaged with Nevirapine Tablets (not EPIVIR-HBV) should be used.

Zidovudine: Patients should be informed that the important toxicities associated with zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV-1 disease.

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 nevirapine 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.

Intensive clinical and laboratory monitoring, including liver enzyme tests, is essential during the first 18 weeks of therapy with nevirapine to detect potentially life-threatening hepatotoxicity and skin reactions. However, liver disease can occur after this period, therefore monitoring should continue at frequent intervals throughout nevirapine treatment. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of hepatic events and skin reactions. Patients with signs and symptoms of hepatitis should discontinue nevirapine and seek medical evaluation immediately. If nevirapine is discontinued due to hepatotoxicity, do not restart it. Patients, particularly women, with increased CD4+ cell count at initiation of nevirapine therapy (>250 cells/mm³ in women and >400 cells/mm³ in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Patients should be advised that co-infection with hepatitis B or C and/or increased transaminase elevations 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).

The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. 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 nevirapine immediately and consult a physician. Nevirapine 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 nevirapine, since nevirapine may lower the plasma levels of these medications. Additionally, when oral contraceptives are used for hormonal regulation during nevirapine therapy, the therapeutic effect of the hormonal therapy should be monitored (see DRUG INTERACTIONS).

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 other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Drug Interactions:

Lamivudine: No change in dose of Trimethoprim/Sulfamethoxazole (TMP/SMX) or lamivudine is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

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

Concomitant use of Lamivudine/Zidovudine with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated *in vitro*. In addition, concomitant use of Lamivudine/Zidovudine with doxorubicin or ribavirin should be avoided because an antagonistic relationship with zidovudine has been demonstrated *in vitro*.

Nevirapine: Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A and 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are metabolized by these enzyme systems may have lower than expected plasma levels when co-administered with nevirapine.

The specific pharmacokinetic changes that occur with co-administration of nevirapine and other drugs are listed in CLINICAL PHARMACOLOGY, Table 3. Clinical comments about possible dosage modifications based on these pharmacokinetic changes are listed in Table 6. The data in Tables 3 and 6 are based on the results of drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

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 Table 7. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in Table 7, 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 6 *Established* Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies (see CLINICAL PHARMACOLOGY, Table 3 for Magnitude of Interaction)

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-intracellular 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	Lopinavir/Ritonavir 400/100 mg tablets can be used twice-daily in combination with nevirapine with no dose adjustment in antiretroviral-naïve patients. A dose increase of Lopinavir/Ritonavir tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with nevirapine in treatment experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence).
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.

Table 7 *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, and Impairment of Fertility:

Carcinogenicity:

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection.

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.

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

Nevirapine: Long-term carcinogenicity studies in mice and rats were carried out with 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. However, 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, is 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.

Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier.

Mutagenicity: Lamivudine: Lamivudine was mutagenic in an L5178Y/TK$^{+/-}$ mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes.

Lamivudine was negative in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Zidovudine: Zidovudine was mutagenic in an L5178Y/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.

Impairment of Fertility: Lamivudine: In a study of reproductive performance, lamivudine, administered to male and female rats at doses up to 130 times the usual adult dose based on body surface area considerations, revealed no evidence of impaired fertility (judged by conception rates) and no effect on the survival, growth, and development to weaning of the offspring.

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

Pregnancy: Pregnancy Category C.

Lamivudine and zidovudine are classified under category C. Nevirapine is classified under category B.

Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets: There are no adequate and well-controlled studies in pregnant women. Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets should be used during pregnancy only if the potential benefits outweigh the potential risk to the fetus.

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

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 those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

Zidovudine: Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/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/day). No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted (see CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY).

Nevirapine: No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. The maternal and developmental no-observable- effect level dosages in rats and rabbits produced systemic exposures approximately equivalent to or approximately 50% higher in rats and rabbits, respectively, than those seen at the recommended daily human dose (based on AUC). In rats, decreased fetal body weights were observed due to administration of a maternally toxic dose (exposures approximately 50% higher than that seen at the recommended human clinical dose).

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status women with CD4 counts >250 cells/mm³ should not initiate nevirapine unless the benefit outweighs the risk to the fetus. It is unclear if pregnancy augments the risk observed in non-pregnant women (see WARNINGS).

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving Lamivudine/Zidovudine Tablets Co- packaged with Nevirapine Tablets.**

Lamivudine/Zidovudine: Lactation studies performed with lamivudine and zidovudine show that both drugs are excreted in human breast milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine. In another study, after administration of a single dose of 200 mg zidovudine to 13 HIV-1-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Nevirapine: Nevirapine is excreted in breast milk.

Pediatric Use: Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine should not be administered to pediatric patients weighing less than 30 kg, because this co-packaged product cannot be adjusted for this patient population.

Geriatric Use: Clinical studies of Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets are not recommended for patients with impaired renal function (i.e., creatinine clearance <50 mL/min; see PRECAUTIONS: Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION) or for patients on hemodialysis.

ADVERSE REACTIONS

Adverse events observed with lamivudine, zidovudine, and nevirapine may be expected with the use of Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets. The adverse events reported with lamivudine, zidovudine, and nevirapine are presented below.

Lamivudine/Zidovudine (Adults):

Lamivudine Plus Zidovudine Administered As Separate Formulations: In 4 randomized, controlled trials of lamivudine 300 mg per day plus zidovudine 600 mg per day, the following selected adverse reactions and laboratory abnormalities were observed (see Tables 8 and 9).

Table 8. Selected Clinical Adverse Events (≥5% Frequency) in 4 Controlled Clinical Trials With lamivudine 300 mg/day and zidovudine 600 mg/day

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

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received lamivudine tablet in controlled clinical trials.

Selected laboratory abnormalities observed during therapy are listed in Table 9.

Table 9. Frequencies of Selected Laboratory Abnormalities Among Adults in 4 Controlled Clinical Trials of lamivudine tablet 300 mg/day plus zidovudine tablet 600 mg/day*

Test (Abnormal Level)	Lamivudine plus Zidovudine % (n)
Neutropenia (ANC<750/mm³)	7.2% (237)
Anemia (Hgb<8.0 g/dL)	2.9% (241)
Thrombocytopenia (platelets<50,000/mm³)	0.4% (240)
ALT (>5.0 x ULN)	3.7% (241)
AST (>5.0 x ULN)	1.7% (241)
Bilirubin (>2.5 x ULN)	0.8% (241)
Amylase (>2.0 x ULN)	4.2% (72)

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

Observed During Clinical Practice: In addition to adverse reactions reported from clinical trials, the following reactions have been identified during post-approval use of lamivudine, zidovudine, and/or lamivudine/zidovudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine, zidovudine, and/or lamivudine/zidovudine.

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

Cardiovascular: Cardiomyopathy.

Endocrine and Metabolic: Gynecomastia, hyperglycemia.

Gastrointestinal: Oral mucosal pigmentation, stomatitis.

General: Vasculitis, weakness.

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

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS).

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness,CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

Nevirapine (Adults): 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).

Skin Reaction: 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 (Trials 1037, 1038, 1046, and 1090), 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.

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

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving nevirapine in placebo-controlled trials are shown in Table 10.

Table 10: Percentage of Patients with Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials

	Trial 1090[1]		Trials 1037,1038, 1046[2]	
	Nevirapine (n=1121)	**Placebo (n=1128)**	**Nevirapine (n=253)**	**Placebo (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
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

1 Background therapy included lamivudine for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm³
2 Background therapy included zidovudine and zidovudine plus didanosine; nevirapine monotherapy was administered in some patients. Patients had CD4+ ell count >200 cells/mm³

Hepatic Reaction: In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4 % (range 0 % to 11 %) of patients who received nevirapine and 1.2 % of patients in control groups. Female gender and higher CD4+ cell 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 > x 5X 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 transaminase elevations 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.

Liver enzyme abnormalities (AST, ALT, GGT) were observed more frequently in patients receiving nevirapine than in controls (see Table 15).

Laboratory Abnormalities: Liver enzyme test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls (Table 15) Asymptomatic elevations in GGT occur frequently but are not a contraindication to continue nevirapine therapy in the absence of elevations in other liver enzyme tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing nevirapine and control regimens (see Table 11).

Table 11 Percentage of Adult Patients with Laboratory Abnormalities

	Trial 1090[1]		Trials 1037, 1038, 1046[2]	
	Nevirapine	**Placebo**	**Nevirapine**	**Placebo**
Laboratory Abnormality	**n=1121**	**n=1128**	**n=253**	**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 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

1 Background therapy included lamivudine for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm³
2 Background therapy included zidovudine and zidovudine plus didanosine; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count >200 cells/mm³

Observed During Clinical Practice

In addition to the adverse reactions reported during clinical trials, the following adverse reactions have been reported during postmarketing use of nevirapine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Gastrointestinal: vomiting

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

Hematology: anemia, eosinophilia, neutropenia

Musculoskeletal: arthralgia, rhabdomyolysis associated with skin and/or liver reactions

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.

In post-marketing surveillance anemia has been more commonly observed in children although development of anemia due to concomitant medication use cannot be ruled out.

OVERDOSAGE

Lamivudine/Zidovudine: There is no known antidote for Lamivudine/Zidovudine.

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

Zidovudine: Acute overdoses of zidovudine have been reported in pediatric patients and adults.These involved exposures up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, confusion, and 1 report of a grand mal seizure. Hematologic changes were transient. All patients recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, GZDV, is enhanced.

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 and Adolescents Weighing ≥30 kg

Lead-in Period (Initial 14 days of dosing):

A 14 day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash. Therefore, the following regimen is recommended for the initial 14 days of dosing:

One Lamivudine/Zidovudine Tablet with one Nevirapine Tablet (containing 150 mg of lamivudine, 300 mg zidovudine and 200 mg of nevirapine) taken once per day followed by a daily oral dose of lamivudine 150 mg and zidovudine 300 mg 12 hours later.

Adults and Adolescents Weighing ≥30 kg

Maintenance:

If the initial 14 days of dosing is tolerated without any incidence of rash, the recommended maintenance oral dose is one Lamivudine/Zidovudine Tablet with one Nevirapine Tablet taken twice daily.

A patient experiencing mild to moderate rash without constitutional symptoms during the 14-day lead-in period of nevirapine 200 mg/day should not have their nevirapine dose increased until the rash has resolved. The total duration of the once daily lead-in dosing period should not exceed 28 days at which point an alternative regimen should be sought.

Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets can be administered with or without food.

Pediatrics

Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets should not be administered to pediatric patients weighing less than 30 kg because this co-packaged product cannot be adjusted for this patient population.

Geriatrics

Although no specific dosage alterations are recommended, caution should be exercised when Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets are administered to geriatric patients (>65 years of age).

Impaired Renal Function

Lamivudine/Zidovudine Tablets Co-Packaged with Nevirapine Tablets are not recommended for patients with impaired renal function (creatinine clearance <50 mL/min) or for patients on hemodialysis.

Impaired Hepatic Function

Lamivudine/Zidovudine Tablets Co-Packaged with Nevirapine Tablets are not recommended for patients with impaired hepatic function.

Monitoring of Patients

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 (see **WARNINGS**). In some cases, hepatic injury has progressed despite discontinuation of treatment.

Lamivudine/Zidovudine Tablets Co-Packaged with Nevirapine Tablets should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings. Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their nevirapine dose increased until the rash has resolved (see **WARNINGS**). Lamivudine/Zidovudine Tablets Co-Packaged with Nevirapine Tablets can cause hepatitis. If clinical hepatitis occurs Lamivudine/Zidovudine Tablets Co-Packaged with Nevirapine Tablets should be discontinued. Do not restart Lamivudine/Zidovudine Tablets Co- Packaged with Nevirapine Tablets after recovery (see **WARNINGS**).

Patients who interrupt Lamivudine/Zidovudine Tablets Co-Packaged with Nevirapine Tablets dosing for more than 7 days should restart with the recommended 14 day lead-in dosing of Lamivudine/Zidovudine Tablets with Nevirapine Tablets once daily followed by a daily dose of lamivudine and zidovudine 12 hours later. After 14 days, maintenance dosing with Lamivudine/Zidovudine Tablets Co-Packaged with Nevirapine Tablets twice daily may be resumed.

HOW SUPPLIED

Lamivudine/Zidovudine Tablets, 150 mg/300 mg Co-packaged with Nevirapine Tablets, 200 mg.

Lamivudine/Zidovudine Tablets 150 mg/300 mg are white, film coated, capsule shaped tablets debossed with 'H' on one side and '2' on other side.

Nevirapine Tablets, 200 mg are Off-white to pale yellow colored, capsule shaped, biconvex tablets debossed with 'H' on one side and '7' on other side with break line on both sides.

Lamivudine/Zidovudine Tablets 150 mg/300 mg Co-packaged with Nevirapine Tablets, 200 mg are supplied in Blisters of 6×10s Blister (PVC/Alu) (NDC 65977-5041-0) and 6×10s Blister (PVC/PVdC) (NDC 65977-5041-1).

Lamivudine/Zidovudine Tablets 150 mg/300 mg Co-packaged with Nevirapine Tablets, 200 mg should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

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- The usual dose of the Lamivudine/Zidovudine Tablets (both the medications are present in one single tablet) for adult and adolescents is one tablet taken twice a day. The usual dose of the co-packaged nevirapine tablets for adults is one tablet daily for the first 14 days followed by one tablet twice daily thereafter. Starting with one Nevirapine Tablet a day for the first 14 days lowers the chance of rash, which could be serious. Therefore, it is important to strictly follow the once daily dose of nevirapine tablets for the first 14 days. Follow your doctor's instructions.
- Take each dose with a full glass of water.
- These medications are taken with or without food.
- Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets are not recommended in children weighing less than 30 kg. Tablets should be taken twice daily with or without food.
- Do not let your Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets run out.
- If you stop taking nevirapine tablets for more than 7 days, ask your doctor before you start taking them again.
- Treatment of HIV/AIDS almost always requires the use of all the three drugs. If you need to stop taking one of the medicines you are taking for HIV, you should stop all of them until you can talk to your doctor.
- Your doctor may want you to have blood tests or other medical evaluations during treatment with this medication to monitor progress and side effects.
- Store these medications at room temperature away from moisture and heat.

Can I take other medicines with Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets?

Other medications may interact with these medications resulting in decreased effectiveness and/or side effects. Talk to your doctor and pharmacist before taking any other prescription or over-the-counter medicines, including vitamins, minerals, and herbal products, during treatment.

- Do **not** take Nizoral® (ketoconazole) or Rifadin®/Rifamate®/Rifater® (rifampin) with nevirapine.
- Tell your doctor if you take Biaxin® (clarithromycin), Diflucan® (fluconazole), methadone, or Mycobutin® (rifabutin). Nevirapine may not be right for you, or you may need careful monitoring.
- It is recommended that you 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 nevirapine. Talk with your doctor about other types of birth control that you can use.

What should I avoid while taking Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets?

Follow your doctor's instructions with respect to high-risk activities such as unprotected sex and personal items that can have blood or body fluids on them, like toothbrushes, razor blades, and needles. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood. These medications do not cure HIV or AIDS and you can still transmit the virus to others during therapy with this medication.

The Centers for Disease Control and Prevention advises mothers with HIV not to breast feed so they will not pass HIV to the infant through their milk. Ask your doctor about the best way to feed your infant.

Avoid alcohol. Alcohol may increase the risk of damage to the pancreas and/or liver.

What are the possible side effects of Lamivudine/Zidovudine Tablets with Nevirapine Tablets?

(Also see **"What is the most important information I should know about Lamivudine/Zidovudine Tablets with Nevirapine Tablets?"** at the beginning of this Medication Guide).

Lamivudine/Zidovudine Tablets can cause

- Serious blood problems including low levels of red and/or white blood cells have occurred with the use of zidovudine. Contact your doctor immediately if you develop unusual fatigue, pale skin, sore throat, fever, or chills which may be signs of blood problems.
- Lactic acidosis and liver problems, including fatal cases, have been reported with the use of reverse transcriptase inhibitors, such as zidovudine and lamivudine, alone or in combination. Contact your doctor immediately if you experience nausea, vomiting, or unusual or unexpected stomach discomfort; weakness and tiredness; shortness of breath; weakness in the arms and legs; yellowing of the skin or eyes; or pain in the upper stomach area. These may be early symptoms of lactic acidosis or liver problems.
- Changes in body fat: These changes have happened in patients taking antiretroviral medicines like lamivudine/zidovudine 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.

If you experience any of the following serious side effects, stop taking this combination of lamivudine and zidovudine and seek emergency medical attention or notify your doctor immediately:

- an allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives);
- muscle pain or weakness; or
- peripheral neuropathy (nerve damage), which may cause numbness, tingling, or pain.

Other, less serious side effects may be more likely to occur.

- mild nausea, vomiting, diarrhea, or decreased appetite;
- a headache;
- dizziness;
- depression/anxiety
- myalgia
- fever
- insomnia

Side effects other than those listed here may also occur. Talk to your doctor about any side effect that seems unusual or that is especially bothersome.

Nevirapine Tablets can cause

- Serious liver damage and skin reactions that can cause death. Any patient can experience such side effects, but some patients are more at risk than others. (See "What is the most important information I should know about lamivudine/ zidovudine tablets co-packaged with nevirapine tablets?" at the beginning of this Medication Guide.)
- Other common side effects of nevirapine include nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain, and myalgia. This list of side effects is not complete. Ask your doctor or pharmacist for more information.
- Changes in body fat have also been seen in some patients taking antiretroviral therapy. 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.

How do I store Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets?

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Throw away medicines that are no longer needed or out-of-date.

Keep all medicines out of the reach of children.

General information about Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use these medications for a condition for which they were not prescribed. Do not give these medications to other people, even if they have the same condition you have. They may harm them.

This Medication Guide summarizes the most important information about Lamivudine/Zidovudine Tablets Co-packaged with Nevirapine Tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about these medications that is written for health professionals

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