

LAMIVUDINE/NEVIRAPINE/ZIDOVUDINE TABLETS

(Lamivudine, Nevirapine and Zidovudine Tablets 150mg/200mg/300mg)

Rx only

WARNING

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

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

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

SEVERE, LIFE-THREATENING, AND IN SOME CASES FATAL HEPATOTOXICITY, PARTICULARLY IN THE FIRST 18 WEEKS, HAS BEEN REPORTED IN PATIENTS TREATED WITH NEVIRAPINE (ONE OF THE COMPONENTS OF LAMIVUDINE/NEVIRAPINE/ZIDOVUDINE). IN SOME CASES, PATIENTS PRESENTED WITH NON-SPECIFIC PRODRIMAL SIGNS OR SYMPTOMS OF HEPATITIS AND PROGRESSED TO HEPATIC FAILURE. THESE EVENTS ARE OFTEN ASSOCIATED WITH RASH. FEMALE GENDER AND HIGHER CD4 COUNTS AT INITIATION OF THERAPY PLACE PATIENTS AT INCREASED RISK; WOMEN WITH CD4 COUNTS >250 CELLS/mm³, INCLUDING PREGNANT WOMEN RECEIVING NEVIRAPINE IN COMBINATION WITH OTHER ANTIRETROVIRALS FOR THE TREATMENT OF HIV INFECTION, ARE AT THE GREATEST RISK. HOWEVER, HEPATOTOXICITY ASSOCIATED WITH NEVIRAPINE USE CAN

OCCUR IN BOTH GENDERS, ALL CD4 COUNTS AND AT ANY TIME DURING TREATMENT. PATIENTS WITH SIGNS OR SYMPTOMS OF HEPATITIS, OR WITH INCREASED TRANSAMINASES COMBINED WITH RASH OR OTHER SYSTEMIC SYMPTOMS, MUST DISCONTINUE NEVIRAPINE 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 NEVIRAPINE 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).

PATIENTS MUST BE MONITORED INTENSIVELY DURING THE FIRST 18 WEEKS OF THERAPY WITH NEVIRAPINE 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 (A COMPONENT OF LAMIVUDINE/NEVIRAPINE/ZIDOVUDINE) FOLLOWING SEVERE HEPATIC, SKIN OR HYPERSENSITIVITY REACTIONS. IN SOME CASES, HEPATIC INJURY HAS PROGRESSED DESPITE DISCONTINUATION OF TREATMENT (SEE WARNINGS).

DESCRIPTION: Lamivudine/ Nevirapine/ Zidovudine: Lamivudine/ nevirapine/zidovudine tablets are combination tablets containing lamivudine, nevirapine and zidovudine. Lamivudine, zidovudine are synthetic nucleoside analogues and nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV.

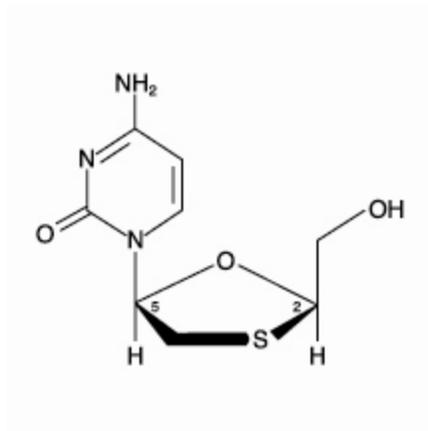
Nevirapine is structurally a member of the dipyrindiazepinone chemical class of compounds.

Lamivudine/Nevirapine/Zidovudine Tablets:

Lamivudine/nevirapine/zidovudine tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 200 mg of nevirapine and 300 mg of zidovudine and the following inactive ingredients: colloidal silicon dioxide, FD&C Blue # 2, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium starch

glycolate, titanium dioxide and triacetin.

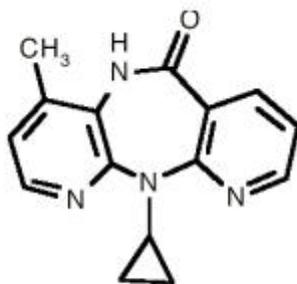
Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$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



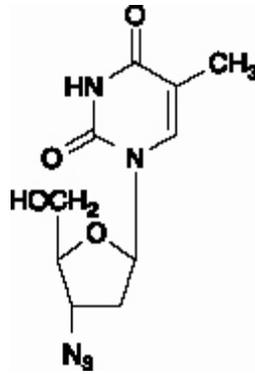
Lamivudine is a white to off-white solid with a solubility of approximately 70 mg/mL in water at 20°C.

Nevirapine:

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



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



Zidovudine is a white to yellowish powder with a solubility of 20.1 mg/mL in water at 25°C.

MICROBIOLOGY

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

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 , γ , or δ) are not inhibited by nevirapine.

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

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. EC₅₀ values (50% effective concentrations) were in the range of 0.003 to 15 μ M (1 μ M = 0.23 mcg/mL). HIV

from therapy-naive subjects with no mutations associated with resistance gave median EC₅₀ values of 0.426 µM (range: 0.200 to 2.007 µM) from Virco (n = 93 baseline samples from COLA40263) and 2.35 µM (1.44 to 4.08 µM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC₅₀ values of lamivudine against different HIV-1 clades (AG) 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.

Nevirapine:

The 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, EC₅₀ values (50% inhibitory concentration) ranged from 14-302 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 EC₅₀ 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 additive 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.

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 EC₅₀ and EC₉₀ values for zidovudine were 0.01 to 0.49 µM (1 µM = 0.27 mcg/mL) and 0.1 to 9 µM, respectively. HIV from therapy-naive subjects with no mutations associated with resistance gave median EC₅₀ values of 0.011 µM (range: 0.005 to 0.110 µM) from Virco (n = 93 baseline samples from COLA40263) and 0.02 µM (0.01 to 0.03 µM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC₅₀ 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, lamivudine, and zalcitabine; 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.

Resistance:

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

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple mutations, the most essential of which may be 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).

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

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 \geq 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 patients experiencing virologic failure (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with Lamivudine and stavudine (study 2NN) for 48 weeks

showed that isolates from 8/25 and 23/46 patients, respectively, contained one or more of the following NNRTI resistance-associated mutations: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

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 mutations 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 mutations.

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

Lamivudine: See Lamivudine Plus Zidovudine (above).

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 NRTI's ddI and ZDV. Similarly, ZDV-resistant isolates were susceptible to nevirapine in cell culture.

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

ANIMAL PHARMACOLOGY

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

CLINICAL PHARMACOLOGY

Matrix Laboratories lamivudine/nevirapine/zidovudine tablets containing lamivudine 150 mg, nevirapine 200 mg and zidovudine 300 mg is bioequivalent to COMBIVIR[®] (lamivudine/zidovudine) tablets of Glaxosmithkline and VIRAMUNE[®] (nevirapine) tablets of Boehringer Ingelheim when administered together in healthy volunteers under both fasting and fed conditions (high fat, high calorie meal).

Pharmacokinetics in Adults:

Lamivudine: The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 1. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. 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).

Nevirapine:

Absorption and Bioavailability of Nevirapine: 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 $93 \pm 9\%$ (mean \pm SD) for a 50 mg tablet. Peak plasma nevirapine concentrations of $2 \pm 0.4 \mu\text{g/mL}$ ($7.5 \mu\text{M}$) 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 $4.5 \pm 1.9 \mu\text{g/mL}$ ($17 \pm 7 \mu\text{M}$), (n = 242) were attained at 400 mg/day. When nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox[®] 30 mL), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate study in HIV-1 infected patients (n=6), nevirapine steady-state systemic exposure (AUC_{τ}) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without food, antacid or didanosine.

Distribution of Nevirapine: Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (V_{dss}) of nevirapine was $1.21 \pm 0.09 \text{ L/kg}$, 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 1-10 $\mu\text{g/mL}$. Nevirapine

concentrations in human cerebrospinal fluid (n=6) were 45% (\pm 5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

Metabolism/Elimination of Nevirapine: *In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A4 and CYP2B6 families, although other isozymes may have a secondary role. In 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 $91.4 \pm 10.5\%$ of the radiolabeled dose was recovered, with urine ($81.3 \pm 11.1\%$) representing the primary route of excretion compared to feces ($10.1 \pm 1.5\%$). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction ($<5\%$) of the radioactivity in urine (representing $<3\%$ of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

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

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	n = 38 [‡]	0.60	n = 39 [§]
	[0.04 to 0.47]		[0.04 to 2.62]	
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.

Effect of Food on Absorption of Lamivudine/Zidovudine:

Lamivudine/zidovudine may be administered with or without food. The extent of lamivudine and zidovudine absorption (AUC) following administration of lamivudine/zidovudine with food was similar when compared to fasting healthy subjects (n = 24).

Special Populations: Impaired Renal Function:

Lamivudine/nevirapine/zidovudine is a fixed dose combination and is not recommended for patients with impaired renal function (creatinine clearance <50 mL/min).

Impaired Hepatic Function:

Lamivudine/nevirapine/zidovudine is a fixed dose combination and is not recommended for patients with impaired hepatic function.

Pregnancy:

See PRECAUTIONS: Pregnancy.

Lamivudine/zidovudine:

No data are available.

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/zidovudine:

No data are available.

Lamivudine: 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.

Zidovudine: After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Pediatric Patients: *Lamivudine/ nevirapine/ zidovudine:* Lamivudine/ nevirapine/ zidovudine should not be administered to pediatric patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

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

Nevirapine: Nevirapine pharmacokinetics in HIV-1-infected adults do 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:* 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.

Nevirapine:

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

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

Drug Interactions: See PRECAUTIONS: Drug Interactions.

Lamivudine/nevirapine/zidovudine:

No drug interaction studies have been conducted using lamivudine/nevirapine/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.

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

Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78% [†]	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64% [†]	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170% [†]	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130% [†]	Not Assessed

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

*This table is not all inclusive.

[†]Estimated range of percent difference.

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/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/HCV co-infected patients (see WARNINGS).

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

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

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)		
				AUC	C _{max}	C _{min}
Antiretrovirals						
Didanosine	100-150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	§
Efavirenz ^a	600 mg QD	200 mg QD x 14 Days; 400 mg QD x 14 days	17	↓28 (↓34 to ↓14)	↓12 (↓23 to ↑1)	↓32 (↓35 to ↓19)
Indinavir ^a	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir ^{a,b}	300/75 mg/m ² (lopinavir/ ritonavir) ^b	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15 ^c	↓22 (↓44 to ↑19)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓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 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Nelfinavir ^a	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	↔	↔	↓32 (↓50 to ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)
Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	↔
Saquinavir ^a	600 mg TID	200 mg QD x 14 days; 200 mg BID x 21 days	23	↓38 (↓47 to ↓11)	↓32 (↓44 to ↓6)	§
Stavudine	30-40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	↔	↔	§
Zalcitabine	0.125-0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	↔	↔	§
Zidovudine	100-200 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓28 (↓40 to ↓4)	↓30 (↓51 to ↑14)	§

Other Medications				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 to ↓24)	↓23 (↓31 to ↓14)	↓56 (↓70 to ↓36)
Metabolite 14-OH-clarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	↔
Ethinyl estradiol ^a and Norethindrone ^a	0.035 mg (as Ortho-Novum [®] 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	↔	§
	1 mg (as Ortho-Novum [®] 1/35)			↓19 (↓30 to ↓7)	↓16 (↓27 to ↓3)	§
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↔	↔	↔
Ketoconazole ^a	400 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	21	↓72 (↓80 to ↓60)	↓44 (↓58 to ↓27)	§
Methadone ^a	Individual Patient Dosing	200 mg QD x 14 days; 200 mg BID ≥7 days	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 to ↑40)	↑28 (↑9 to ↑51)	↔
Metabolite 25-O-desacetyl-rifabutin				↑24 (↓16 to ↑84)	↑29 (↓2 to ↑68)	↑22 (↓14 to ↑74)
Rifampin ^a	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑11 (↓4 to ↑28)	↔	§

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

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

^a For information regarding clinical recommendations see **PRECAUTIONS, Drug Interactions, Table 6.**

^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 effect of other drugs listed in Table 3 on nevirapine pharmacokinetics was not significant.

INDICATIONS AND USAGE

Lamivudine/nevirapine/zidovudine 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/nevirapine/zidovudine 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**).
- The 14-day lead-in period with nevirapine 200 mg 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 nevirapine 200 mg twice daily. The nevirapine 200 mg once daily dosing regimen should not be continued beyond 28 days at which point an alternative regimen should be sought.

Description of Clinical Studies:

Lamivudine Plus Zidovudine: The NUCB3007 (CAESAR) study was conducted using EPIVIR 150-mg Tablets (150 mg twice daily) and RETROVIR 100-mg Capsules (2 x 100 mg 3 times daily). CAESAR was a multi-center, double-blind, placebo-controlled study comparing continued current therapy [zidovudine alone (62% of patients) or zidovudine with didanosine or zalcitabine (38% of patients)] to the addition of EPIVIR or EPIVIR plus an investigational non-nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1,816 HIV-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)	EPIVIR plus Current Therapy (n = 896)	EPIVIR 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 log₁₀ 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+ddl 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+ddl patients. The nevirapine + ZDV group mean decreased by 6 cells/mm³ below baseline.

CONTRAINDICATIONS

Lamivudine/nevirapine/zidovudine tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product.

WARNINGS

Lamivudine/nevirapine/zidovudine is a fixed-dose combination of lamivudine, nevirapine and zidovudine. Ordinarily, lamivudine/nevirapine/zidovudine should not be administered concomitantly with lamivudine, nevirapine, zidovudine, EPZICOMTM, a fixed-dose combination of abacavir and lamivudine, or TRIZIVIR[®], a fixed-dose combination of abacavir, lamivudine, and zidovudine.

The complete prescribing information for all agents being considered for use with lamivudine/ nevirapine/zidovudine should be consulted before combination therapy with lamivudine/ nevirapine/zidovudine is initiated.

Lamivudine/zidovudine:

Bone Marrow Suppression: Lamivudine/ zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count $<1,000$ cells/mm³ or hemoglobin <9.5 g/dL (see ADVERSE REACTIONS).

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with lamivudine/zidovudine. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

Lactic Acidosis/Severe Hepatomegaly With Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine, and other antiretrovirals. A majority of these cases have been in women. 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 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-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 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of 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/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine or zidovudine in HIV/HCV co-infected patients (see CLINICAL PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and lamivudine/nevirapine/zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of lamivudine/ nevirapine/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 >6) (see the complete prescribing information for interferon and ribavirin).

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 lifethreatening hepatic events and skin reactions. The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation and at two weeks post-dose escalation. After the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment. In addition, the 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash.

Hepatic Events

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

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

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

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

The patients at greatest risk of hepatic events, including potentially fatal events, are women with high CD4 counts. In general, during the first 6 weeks of treatment, women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4 counts >250 cells/mm³ had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts <250 cells/mm³ (11.0% versus 0.9%). An increased risk was observed in men with CD4 counts >400 cells/mm³ (6.3% versus 1.2% for men with CD4 counts <400 cells/mm³). However, all patients, regardless of gender, CD4 count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events

have been reported at all CD4 counts. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

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

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 CLINICAL PHARMACOLOGY, *Pharmacokinetics in Special Populations: Hepatic Impairment*; PRECAUTIONS, *General*).

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 or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue nevirapine and seek medical evaluation immediately (see **PRECAUTIONS, *Information for Patients***). Do not restart lamivudine/nevirapine/zidovudine 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 nevirapine.

Therapy with nevirapine must be initiated with a 14-day lead-in period of 200 mg/day, 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 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 (see **DOSAGE AND ADMINISTRATION**). Patients should be monitored closely if isolated rash of any severity occurs. Delay in stopping nevirapine 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.

St. John's wort

Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort containing products and nevirapine is not recommended. Co-administration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in sub-optimal levels of nevirapine and lead to loss of virologic response and possible resistance to nevirapine or to the class of NNRTIs.

PRECAUTIONS: Lamivudine/zidovudine:

Patients With HIV 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 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).

Patients With Impaired Renal Function: Patients with creatinine clearance <50 mL/min should not receive lamivudine/nevirapine/zidovudine tablets.

Patients With Impaired Hepatic Function: Lamivudine/ nevirapine/ zidovudine tablets are not recommended for patients with impaired hepatic function.

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**).

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, do not administer nevirapine to patients with moderate or severe (Child Pugh Class B or C, respectively) hepatic impairment (see **WARNINGS; CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations: Hepatic Impairment**).

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 infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

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

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

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

Information for Patients: Lamivudine/nevirapine/zidovudine tablets are not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should

be advised that the use of lamivudine/nevirapine/zidovudine tablets has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be advised of the importance of taking lamivudine/nevirapine/zidovudine tablets exactly as it is prescribed.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Lamivudine: Patients co-infected with HIV and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician.

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 function 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 liver function tests at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT (see **WARNINGS, Hepatic Events**).

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 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 **PRECAUTIONS, Drug Interactions**).

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

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

Patients should be informed to take nevirapine 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.

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 disease.

Drug Interactions: Lamivudine: Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY). No data are available regarding the potential for interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

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

Nevirapine:

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A4 and 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are metabolized by these enzyme systems may have lower than expected plasma levels when coadministered 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 ↑ 14-OH clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against <i>Mycobacterium avium-intracellulare complex</i> , 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	<p>KALETRA 400/100 mg tablets can be used twice-daily in combination with nevirapine with no dose adjustment in antiretroviral-naïve patients.</p> <p>A dose increase of KALETRA 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).</p> <p>A dose increase of lopinavir/ritonavir oral solution to 533/133 mg twice daily with food is recommended in combination with nevirapine.</p> <p>In children 6 months to 12 years of age, consideration should be given to increasing the dose of lopinavir/ritonavir to 13/3.25 mg/kg for those 7 to < 15 kg; 11/2.75 mg/kg for those 15 to 45 kg; and up to a maximum dose of 533/133 mg for those > 45 kg twice daily when used in combination with nevirapine, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.</p>
Methadone	↓Methadone	Methadone levels were 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.

Table 7 Potential Drug Interactions: Use With Caution, Dose Adjustment of Co-administered Drug May Be Needed due to Possible Decrease in Clinical Effect

Examples of Drugs in Which Plasma Concentrations May Be Decreased By Co-administration With Nevirapine	
Drug Class	Examples of Drugs
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.

Zidovudine: Coadministration of ganciclovir, interferon alfa, 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*.

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 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.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months at the highest dose, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of

gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

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

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.

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.

Pregnancy: *Pregnancy Category C.*

Lamivudine/zidovudine: There are no adequate and well-controlled studies of lamivudine/zidovudine in pregnant women. Reproduction studies with lamivudine and zidovudine have been performed in animals (see Lamivudine and Zidovudine sections below). Lamivudine/zidovudine should be used during pregnancy only if the potential benefits outweigh the risks.

Lamivudine: Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at 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 embryoletality 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.

Zidovudine: Reproduction studies with orally administered zidovudine 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 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. 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).

Pregnancy Category B

Nevirapine:

No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. The maternal and developmental no-observable-effect level dosages 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).

There are no adequate and well-controlled studies of nevirapine in pregnant women. The Antiretroviral Pregnancy Registry, which has been surveying pregnancy outcomes since January 1989, has not found an increased risk of birth defects following first trimester exposures to nevirapine. The prevalence of birth defects after any trimester exposure to nevirapine is comparable to the prevalence observed in the general population.

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

Nevirapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV 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 breast-feed if they are receiving lamivudine/ nevirapine/ zidovudine tablets.

Lamivudine/zidovudine: No specific studies of lamivudine and zidovudine excretion in breast milk after dosing with lamivudine/zidovudine have been performed. Lamivudine and zidovudine are excreted in human breast milk (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Nursing Mothers). A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma.

Nevirapine

Nevirapine is excreted in breast milk.

Pediatric Use: Lamivudine/ nevirapine/zidovudine tablets should not be administered to pediatric patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

Geriatric Use: *Lamivudine/nevirapine/zidovudine:* Clinical studies of lamivudine/nevirapine/zidovudine 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/nevirapine/zidovudine is 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).

ADVERSE REACTIONS

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

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

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

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received EPIVIR 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 EPIVIR 300 mg/day plus RETROVIR 600 mg/day*

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

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

n = Number of patients assessed.

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

Nevirapine:

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

Adults

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

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

Asymptomatic transaminase elevations (AST or ALT > 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

liver function tests at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

Liver enzyme abnormalities (AST, ALT, GGT) were observed more frequently in patients receiving nevirapine than in controls (see Table 11).

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	Placebo	Nevirapine	Placebo
	(n=1121)	(n=1128)	(n=253)	(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	2.0

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

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

Laboratory Abnormalities: Liver function test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls (Table 11). Asymptomatic elevations in GGT occur frequently but are not a reason to stop nevirapine therapy in the absence of elevations in other liver function tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing nevirapine and control regimens (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 <8.0 g/dL	3.2	4.1	0	0
Platelets <50,000/mm ³	1.3	1.0	0.4	1.5
Neutrophils <750/mm ³	13.3	13.5	3.6	1.0

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

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

Observed During Clinical Practice: *Lamivudine/zidovudine*: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of EPIVIR, RETROVIR, 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 EPIVIR, RETROVIR, 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: In addition to the adverse events identified during clinical trials, the following events have been reported with the use of nevirapine in clinical practice:

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

OVERDOSAGE

Lamivudine/nevirapine/zidovudine: There is no known antidote for lamivudine/nevirapine/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.

Nevirapine:

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.

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.

DOSAGE AND ADMINISTRATION

Adults

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/nevirapine/zidovudine tablet (containing 150 mg of lamivudine, 200 mg of nevirapine and 300 mg of zidovudine) taken once per day followed by a daily oral dose of lamivudine 150 mg and zidovudine 300 mg 12 hours later.

Adults

Maintenance:

If the initial 14 days of dosing is tolerated without any incidence of rash, the recommended maintenance oral dose is one lamivudine/nevirapine/zidovudine 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.

Pediatrics:

Lamivudine/nevirapine/zidovudine tablets should not be administered to pediatric patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

Geriatrics:

Although no specific dosage alterations are recommended, caution should be exercised when lamivudine/nevirapine/zidovudine tablets are administered to geriatric patients (>65 years of age).

Impaired Renal Function:

Lamivudine/nevirapine/zidovudine is a fixed dose combination and is not recommended for patients with impaired renal function (creatinine clearance <50 mL/min).

Impaired Hepatic Function:

Lamivudine/nevirapine/zidovudine is a fixed dose combination and is 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.

HOW SUPPLIED

Lamivudine/nevirapine/zidovudine tablets 150 mg/200 mg/300 mg are blue colored, capsule shaped, biconvex, film coated tablets, debossed with “M” and “104” on one side and plain on other side. They are available as follows:

Bottles of 60 tablets
Unit dose tablets 60's (6x10)

NDC 65015-036-05
NDC 65015-036-17

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature]. Store in a safe place out of the reach of children.



Matrix Laboratories Limited.
Secunderabad, INDIA.

October 2008

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

Rx Only

MEDICATION GUIDE

LAMIVUDINE/NEVIRAPINE/ZIDOVUDINE TABLETS

Read this Medication Guide before you start taking lamivudine/nevirapine/zidovudine 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/nevirapine/zidovudine tablets when you start taking your medicine and at regular checkups. You should stay under a doctor's care while using lamivudine/ nevirapine/zidovudine 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/nevirapine/ zidovudine tablets?

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

Liver Reactions

Any patient can experience liver problems while taking 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 function 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 lamivudine/nevirapine/zidovudine tablets and call your doctor right away:

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

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

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

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

These are not all the side effects of nevirapine. See the section "**What are the possible side effects of nevirapine?**" for more information. Tell your doctor if you have any side effects from nevirapine.

What is nevirapine, lamivudine and zidovudine (the components of lamivudine/nevirapine/zidovudine tablets)?

Nevirapine, lamivudine and zidovudine are medicines used to treat Human Immunodeficiency Virus (HIV), the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

Nevirapine is a type of anti-HIV medicine called a "non-nucleoside reverse transcriptase inhibitor" (NNRTI). Lamivudine and zidovudine are both nucleoside reverse transcriptase inhibitors. All three medicines work by lowering the amount of HIV in the blood ("viral load"). These three medicines 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/nevirapine/zidovudine may not have these effects in every patient.

do not cure HIV or AIDS, and it is not known if it will help you live longer with HIV. People taking lamivudine/nevirapine/zidovudine 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.

Who should not take lamivudine/ nevirapine/zidovudine tablets?

- Do not take nevirapine if you are allergic to lamivudine or nevirapine or zidovudine or any of its ingredients. The active ingredients are lamivudine, nevirapine and zidovudine. Your doctor or pharmacist can tell you about the inactive ingredients.
- Do not restart nevirapine (one of the component of lamivudine/nevirapine/zidovudine tablet) after you recover from serious liver or skin reactions that happened when you took nevirapine.
- Do not take lamivudine/nevirapine/zidovudine tablets if you have severe liver problems.
- Do not take nevirapine if you take certain medicines. (See “**Can I take other medicines with nevirapine?**” for a list of medicines.)
- Do not take nevirapine if you are not infected with HIV.

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

Before starting nevirapine one of the component of lamivudine/nevirapine/zidovudine tablet), tell your doctor about all of your medical conditions, including if you:

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

How should I take lamivudine/ nevirapine/ zidovudine tablets?

Adults

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

A 14 day lead-in period with nevirapine 200 mg daily dosing lowers the chances of getting a rash. Therefore, do the following for the initial 14 days of dosing:

Take one lamivudine/nevirapine/zidovudine tablet (containing 150 mg of lamivudine, 200 mg of nevirapine and 300 mg of zidovudine) once per day followed by a daily oral dose of lamivudine 150 mg and zidovudine 300 mg 12 hours later.

Adults

Maintenance (after the first 14 days):

If the initial 14 days of dosing is tolerated without any incidence of rash, the recommended oral dose is one lamivudine/nevirapine/zidovudine tablet taken twice daily.

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

Can I take other medicines with lamivudine/ nevirapine/zidovudine tablets)?

- Nevirapine (one of the component of lamivudine/nevirapine/zidovudine tablets) may change the effect of other medicines, and other medicines can change the effect of nevirapine. Tell your doctors and pharmacists about **all** medicines you take, including non-prescription medicines, vitamins and herbal supplements.
- Do **not** take Nizoral[®] (ketoconazole) or Rifadin[®]/Rifamate[®]/Rifater[®] (rifampin) with 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/nevirapine/zidovudine tablets?

Avoid doing things that can spread HIV infection, as lamivudine/nevirapine/zidovudine tablets do not stop you from passing HIV infection to others. Do not share needles, other injection equipment or personal items that can have blood or body fluids on them, like toothbrushes and razor

blades. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

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.

What are the possible side effects of nevirapine (a component of lamivudine/ nevirapine/zidovudine tablets)?

Nevirapine 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/nevirapine/zidovudine tablets?**" at the beginning of this Medication Guide.

Other common side effects of nevirapine (one of the component of lamivudine/nevirapine/zidovudine tablets) 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/ nevirapine/ zidovudine tablets?

Store lamivudine/nevirapine/zidovudine tablets at **25°C (77°F); excursions permitted to 15°–30°C (59°–86°F)** [see USP Controlled Room Temperature]. Throw away lamivudine/ nevirapine/zidovudine that is no longer needed or out-of-date.

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

General information about lamivudine/nevirapine/zidovudine tablets

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

This Medication Guide summarizes the most important information about lamivudine/nevirapine/zidovudine tablets. If you would like more information, talk

with your doctor. You can ask your pharmacist or doctor for information about lamivudine/nevirapine/zidovudine tablets that is written for health professionals.

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



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October 2008