

## **PRESCRIBING INFORMATION**

### **Lamivudine, Stavudine and Nevirapine Tablets**

(Lamivudine 150 mg, Stavudine 30 mg and Nevirapine 200 mg)

(Lamivudine 150 mg, Stavudine 40 mg and Nevirapine 200 mg)

Rx Only

#### **WARNINGS**

**SEVERE, LIFE THREATENING, AND IN SOME CASES FATAL HEPATOTOXICITY, PARTICULARLY IN THE FIRST 18 WEEKS, HAS BEEN REPORTED IN PATIENTS TREATED WITH NEVIRAPINE. IN SOME CASES, PATIENTS PRESENTED WITH NON-SPECIFIC PRODROMAL SIGNS OR SYMPTOMS OF HEPATITIS AND PROGRESSED TO HEPATIC FAILURE. THESE EVENTS ARE OFTEN ASSOCIATED WITH RASH. FEMALE GENDER AND HIGHER CD4+ CELL COUNTS AT INITIATION OF THERAPY PLACE PATIENTS AT INCREASED RISK; WOMEN WITH CD4+ CELL COUNTS > 250 CELLS/MM<sup>3</sup>, INCLUDING PREGNANT WOMEN RECEIVING NEVIRAPINE IN COMBINATION WITH OTHER ANTIRETROVIRALS FOR THE TREATMENT OF HIV-1 INFECTION, ARE AT THE GREATEST RISK. HOWEVER, HEPATOTOXICITY ASSOCIATED WITH NEVIRAPINE USE CAN OCCUR IN BOTH GENDERS, ALL CD4+ CELL COUNTS AND AT ANY TIME DURING TREATMENT. PATIENTS WITH SIGNS OR SYMPTOMS OF HEPATITIS, OR WITH INCREASED TRANSAMINASES COMBINED WITH RASH OR OTHER SYSTEMIC SYMPTOMS, MUST DISCONTINUE 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 AS SOON AS POSSIBLE AND SEEK MEDICAL ATTENTION (SEE WARNINGS AND PRECAUTIONS).**

**IT IS ESSENTIAL THAT PATIENTS 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 FOLLOWING SEVERE HEPATIC, SKIN OR HYPERSENSITIVITY REACTIONS. IN SOME CASES, HEPATIC INJURY HAS PROGRESSED DESPITE DISCONTINUATION OF TREATMENT. IN ADDITION, THE 14-DAY LEAD-IN PERIOD WITH NEVIRAPINE 200 MG DAILY DOSING MUST BE STRICTLY FOLLOWED (SEE WARNINGS AND PRECAUTIONS).**

**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, STAVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS)**

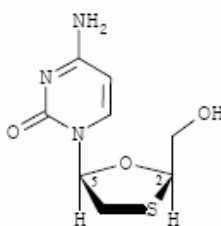
**SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV-1 AND HAVE DISCONTINUED LAMIVUDINE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVUDINE AND ARE CO-INFECTED WITH HIV-1 AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).**

## DESCRIPTION

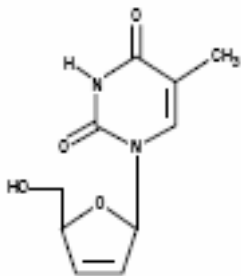
Lamivudine, Stavudine and Nevirapine Tablets contain a fixed dose combination of lamivudine, stavudine and nevirapine. Both stavudine and lamivudine belong to the synthetic nucleoside analogue class of antiretroviral drugs. Both drugs act by terminating the growth of the DNA chain and inhibiting the reverse transcriptase of HIV. Nevirapine is a non-nucleoside reverse transcriptase inhibitor specific for HIV-1 reverse transcriptase.

Lamivudine, Stavudine and Nevirapine Tablets are for oral administration. The fixed dose tablets contain active ingredients lamivudine 150 mg, stavudine 30 mg/40 mg, and nevirapine 200 mg. The inactive ingredients are microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, colour iron oxide yellow, povidone, colloidal anhydrous silica, lactose, talc and magnesium stearate.

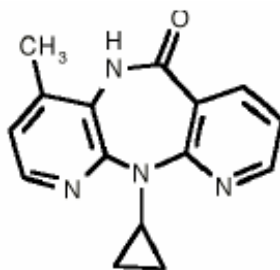
**Lamivudine** - The chemical name of lamivudine is (2R-cis)-4-amino-1- [2-(hydroxymethyl)-1,3-oxanthiolan-5-yl]-pyrimidinone. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of  $C_8H_{11}N_3O_3S$  and a molecular weight of 229.3. Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C. It has the following structural formula:



**Stavudine** - The chemical name for stavudine is 2', 3'-dideoxy-3'-deoxythymidine. The molecular formula of stavudine is  $C_{10}H_{12}N_2O_4$  and its molecular weight is 224.2. Stavudine is a white to off-white crystalline solid and its solubility at 23°C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23°C is 0.144. It has the following structural formula:



**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. The molecular formula is  $C_{15}H_{14}N_4O$  and the molecular weight is 266.30. Nevirapine is a white to off-white crystalline solid with a solubility of approximately 0.05 mg/mL in water at 25°C. Nevirapine has the following structural formula:



## 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 the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases  $\alpha$ ,  $\beta$  and  $\gamma$ .

**Stavudine** - Stavudine, a nucleoside analogue of thymidine, is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate thymidine triphosphate ( $K_i=0.0083$  to  $0.032 \mu\text{M}$ ) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases  $\beta$  and  $\gamma$  and markedly reduces the synthesis of mitochondrial DNA.

**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  $\alpha$ ,  $\beta$ ,  $\gamma$ , or  $\delta$ ) are not inhibited by nevirapine.

***Antiviral activity:***

**Lamivudine** - The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC<sub>50</sub> values (50% effective concentrations) were in the range of 0.003 to 15  $\mu$ M (1  $\mu$ M = 0.23 mcg/mL). The EC<sub>50</sub> values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120  $\mu$ M, and against HIV-2 isolates from 0.003 to 0.120  $\mu$ M. Ribavirin (50  $\mu$ M) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold. In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. Please see the EPIVIR-HBV package insert for information regarding the inhibitory activity of lamivudine against HBV.

**Stavudine** - The antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit HIV-1 replication by 50% (EC<sub>50</sub>) ranged from 0.009 to 4  $\mu$ M against laboratory and clinical isolates of HIV-1. In cell culture, stavudine exhibited additive to antagonistic anti-HIV-1 activity in combination with zidovudine. Stavudine in combination with either abacavir, didanosine, tenofovir, or zalcitabine exhibited additive to synergistic activity. Ribavirin, at the 9-45  $\mu$ M concentrations tested, reduced the anti-HIV-1 activity of stavudine by 2.5- to 5-fold.

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

***Resistance:***

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

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. 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.

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

**Stavudine** - HIV-1 isolates with reduced susceptibility to stavudine have been selected in cell culture (strain-specific) and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV-1 isolates from 61 patients receiving prolonged (6 to 29 months) stavudine monotherapy showed that post-therapy isolates from four patients exhibited EC<sub>50</sub> values more than 4-fold (range 7- to 16-fold) higher than the average pretreatment susceptibility of baseline isolates. Of these, HIV-1 isolates from one patient contained the zidovudine-resistance-associated mutations T215Y and K219E, and isolates from another patient contained the multiple-nucleoside-resistance-associated mutation Q151M. Mutations in the RT gene of HIV-1 isolates from the other two patients were not detected.

**Nevirapine** - HIV-1 isolates with reduced susceptibility (100- to 250-fold) to nevirapine have been selected 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.

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

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve patients receiving either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase I/II trials over 1 to  $\geq$ 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 virologic failure patients (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine (study 2NN) for 48 weeks showed that isolates from 8/25 and 23/46 patients, respectively, contained one or more of the following NNRTI resistance-associated **substitutions**: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

***Cross-Resistance:***

**Lamivudine** - Cross-resistance among HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs) has been observed. Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

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

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

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

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

**Stavudine** - Several studies have demonstrated that prolonged stavudine treatment can select and/or maintain mutations associated with zidovudine resistance. HIV-1 isolates with one or more zidovudine-resistance-associated **substitutions** (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) exhibited reduced susceptibility to stavudine in cell culture.

**Nevirapine** - Cross-resistance among HIV-1 nonnucleoside analog reverse transcriptase inhibitors (NNRTIs) has been observed. 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.

## CLINICAL PHARMACOLOGY

### Pharmacokinetics in Adults:

The rate and extent of absorption of Lamivudine, Stavudine, and Nevirapine from the combination tablets was similar to that from Epivir<sup>®</sup> tablets, Zerit<sup>®</sup> capsules, and Viramune<sup>®</sup> tablets respectively, when administered to healthy volunteers in the fasted state.

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

**Distribution:** The apparent volume of distribution after IV administration of lamivudine to 20 patients was  $1.3 \pm 0.4$  L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. Binding of lamivudine to human plasma proteins is low (<36%).

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

**Elimination:** The majority of lamivudine is eliminated unchanged in urine. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was  $199.7 \pm 56.9$  mL/min (mean  $\pm$  SD). In most single-dose studies in HIV-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ( $t_{1/2}$ ) ranged from 5 to 7 hours. In HIV-infected patients, total clearance was  $398.5 \pm 69.1$  mL/min (mean  $\pm$  SD).

**Stavudine – Absorption and Bioavailability:** Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The oral bioavailability of stavudine is  $86.4 \pm 18.2\%$ . The systemic exposure to stavudine is the same following administration as capsules or solution.

**Distribution:** Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4  $\mu$ g/mL. Stavudine distributes equally between red blood cells and plasma. The apparent oral volume of distribution is  $66 \pm 22$  L.

**Metabolism:** The metabolic fate of stavudine has not been elucidated in humans.

**Elimination:** Renal elimination accounted for about 40% of the overall clearance regardless of the route of administration. The mean renal clearance was about twice the

average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration. Elimination half – life for oral dose  $1.44 \pm 0.30$  hours.

***Nevirapine - Absorption and Bioavailability:*** Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was  $93 \pm 9\%$  (mean  $\pm$  SD) for a 50 mg tablet and  $91 \pm 8\%$  for an oral solution. 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. Nevirapine may be administered with or without antacid or didanosine.

***Distribution:*** Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution ( $V_{\text{dss}}$ ) 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. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1 to 10 mcg/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:*** *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. Cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans.

Nevirapine is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A4 and 2B6. 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 to 30 hours following multiple dosing with 200 to 400 mg/day.

### **Effect of Food on Absorption of Lamivudine/Stavudine/Nevirapine.**

The effect of food on the rate and extent of absorption of Lamivudine/Stavudine/Nevirapine combination tablets has not been evaluated in a clinical study. Therefore, Lamivudine/Stavudine/Nevirapine combination tablets should be taken under fasting conditions.

### **Special Populations:**

#### ***Impaired renal function:***

Lamivudine/Stavudine/Nevirapine Tablets are not recommended for patients with impaired renal function (see DOSAGE and ADMINISTRATION: PRECAUTIONS)



***Impaired hepatic function:***

Lamivudine/Stavudine/Nevirapine Tablets are not recommended for patients with impaired hepatic function.

***Pregnancy:*** See PRECAUTIONS: Pregnancy

Lamivudine/Stavudine/Nevirapine Tablets: No data available.

***Nursing Mothers:*** See PRECAUTIONS: Nursing Mothers

***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.

***Stavudine:*** No data is available on pharmacokinetics of stavudine in nursing mothers. It is not known whether stavudine is excreted in breast milk.

***Nevirapine:*** No data is available on pharmacokinetics of nevirapine in nursing mothers. Nevirapine is excreted in human milk.

***Pediatric Patients:***

Lamivudine, Stavudine and Nevirapine Tablets are recommended in pediatric patients >12 years of age and weighing  $\geq$  50kg.

***Geriatric Patients:***

The pharmacokinetics of lamivudine and stavudine 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:*** There are no significant gender differences in lamivudine pharmacokinetics.

***Stavudine:*** A population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between males (n=291) and females (n=27).

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

***Race:***

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

**Stavudine:** A population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between races (n=233 Caucasian, 39 African-American, 41 Hispanic, 1 Asian, and 4 other).

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

**Drug Interactions:**

**No drug interaction studies have been conducted with the Lamivudine/Stavudine/Nevirapine Tablets.**

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

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended. There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects.

**Stavudine:** Zidovudine competitively inhibits the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine should be avoided.

*In vitro* data indicate that the phosphorylation of stavudine is inhibited at relevant concentrations by doxorubicin and ribavirin.

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Because stavudine is not protein-bound, it is not expected to affect the pharmacokinetics of protein-bound drugs.

Tables 1 and 2 summarize the effects on AUC and C<sub>max</sub>, with a 95% confidence interval (CI) when available, following co-administration of stavudine with didanosine, lamivudine, and nelfinavir. No clinically significant pharmacokinetic interactions were observed.

**Table 1: Results of Drug Interaction Studies with Stavudine: Effects of Co-administered Drug on Stavudine Plasma AUC and C<sub>max</sub> Values**

Drug	Stavudine Dosage	n <sup>a</sup>	AUC of Stavudine (95% CI)	C <sub>max</sub> of Stavudine (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↑ 17%
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (92.7-100.6%)	↑ 12% (100.3-126.1%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔
↑ indicates increase.				
↔ indicates no change, or mean increase or decrease of <10%.				
<sup>a</sup> HIV-infected patients.				

**Table 2: Results of Drug Interaction Studies with Stavudine: Effects of Stavudine on Co-administered Drug Plasma AUC and C<sub>max</sub> Values**

Drug	Stavudine Dosage	n <sup>a</sup>	AUC of Co-administered Drug (95% CI)	C <sub>max</sub> of Co-administered Drug (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↔
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (90.5-107.6%)	↔ (87.1-110.6%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

↔ indicates no change, or mean increase or decrease of <10%.

<sup>a</sup> HIV-infected patients.

**Nevirapine:** 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 Ki for the inhibition of CYP3A4 was 270 μmol, a concentration that is unlikely to be achieved in patients as the therapeutic range is <25 μmol. 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<sub>max</sub>, and C<sub>min</sub> 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 <sub>max</sub>	C <sub>min</sub>
Antiretrovirals				AUC	C <sub>max</sub>	C <sub>min</sub>
Didanosine	100-150 mg BID	200 mg QD × 14 days; 200 mg BID × 14 days	18	↔	↔	§
Efavirenz <sup>a</sup>	600 mg QD	200 mg QD × 14 days; 400 mg QD × 14 days	17	↓28 (↓34 - ↓14)	↓12 (↓23 - ↑1)	↓32 (↓35 - ↓19)
Indinavir <sup>a</sup>	800 mg q8H	200 mg QD × 14 days; 200 mg BID × 14 days	19	↓31 (↓39 - ↓22)	↓15 (↓24 - ↓4)	↓44 (↓53 - ↓33)
Lopinavir <sup>a, b</sup>	300/75 mg/m <sup>2</sup>	7 mg/kg or 4	12,	↓14	↓22	↓55

	(lopinavir/ritonavir) <sup>b</sup>	mg/kg QD × 15 <sup>c</sup> 2 weeks; BID × 1 week		(↓ 36 - ↑ 16)	(↓ 44 - ↑ 9)	(↓ 75 - ↓ 9)
Lopinavir <sup>a</sup>	400/100 mg BID (lopinavir/ritonavir)	200 mg QD × 14 days; 200 mg BID > 1 year	22, 19 <sup>c</sup>	↓ 27 (↓ 47 - ↓ 2)	↓ 19 (↓ 38 - ↑ 5)	↓ 51 (↓ 72 - ↓ 26)
Nelfinavir <sup>a</sup>	750 mg TID	200 mg QD × 14 days; 200 mg BID × 14 days	23	↔	↔	↓ 32 (↓ 50 - ↑ 5)
Nelfinavir-M8 metabolite				↓ 62 (↓ 70 - ↓ 53)	↓ 59 (↓ 68 - ↓ 48)	↓ 66 (↓ 74 - ↓ 55)
Ritonavir	600 mg BID	200 mg QD × 14 days; 200 mg BID × 14 days	18	↔	↔	↔
Saquinavir <sup>a</sup>	600 mg TID	200 mg QD × 14 days; 200 mg BID × 21 days	23	↓ 38 (↓ 47 - ↓ 11)	↓ 32 (↓ 44 - ↓ 6)	§
Stavudine	30-40 mg BID	200 mg QD × 14 days; 200 mg BID × 14 days	22	↔	↔	§
Zalcitabine	0.125-0.25 mg TID	200 mg QD × 14 days; 200 mg BID × 14 days	6	↔	↔	§
Zidovudine	100-200 mg TID	200 mg QD × 14 days; 200 mg BID × 14 days	11	↓ 28 (↓ 40 - ↓ 4)	↓ 30 (↓ 51 - ↑ 14)	§
Other Medications				AUC	C <sub>max</sub>	C <sub>min</sub>
Clarithromycin <sup>a</sup>	500 mg BID	200 mg QD × 14 days; 200 mg BID × 14 days	15	↓ 31 (↓ 38 - ↓ 24)	↓ 23 (↓ 31 - ↓ 14)	↓ 57 (↓ 70 - ↓ 36)
Metabolite 14- OH- clarithromycin				↑ 42 (↑ 16 - ↑ 73)	↑ 47 (↑ 21 - ↑ 80)	↔
Ethinyl estradiol <sup>a</sup> and Norethindrone <sup>a</sup>	0.035 mg (as Ortho- Novum <sup>®</sup> 1/35) 1 mg (as Ortho- Novum <sup>®</sup> 1/35)	200 mg QD × 14 days; 200 mg BID × 14 days	10	↓ 20 (↓ 33 to ↓ 3)	↔	§
Fluconazole	200 mg QD	200 mg QD	19	↔	↔	↔

		× 14 days; 200 mg BID × 14 days				
Ketoconazole <sup>a</sup>	400 mg QD	200 mg QD × 14 days; 200 mg BID × 14 days	21	↓72 (↓ 80 - ↓ 60)	↓44 (↓ 58 - ↓ 27)	§
Rifabutin <sup>a</sup>	150 or 300 mg QD	200 mg QD × 14 days; 200 mg BID × 14 days	19	↑17 (↓ 2 - ↑ 40)	↑28 (↑ 9 - ↑ 51)	↔
Metabolite 25-O-desacetyl-rifabutin				↑24 (↓ 16 - ↑ 84)	↑29 (↓ 2 - ↑ 68)	↑22 (↓14 - ↑74)
Rifampin <sup>a</sup>	600 mg QD	200 mg QD × 14 days; 200 mg BID × 14 days	14	↑11 (↓ 4 - ↑ 28)	↔	§
§ = C <sub>min</sub> below detectable level of the assay						
↑ = Increase, ↓ = Decrease, ↔ = No Effect						
<sup>a</sup> For information regarding clinical recommendations see Drug Interactions						
<sup>b</sup> Pediatric subjects ranging in age from 6 months to 12 years						
<sup>c</sup> Parallel group design; n for nevirapine +lopinavir/ritonavir, n for lopinavir/ritonavir alone						

## INDICATIONS AND USAGE

Lamivudine, Stavudine and Nevirapine Tablets are indicated for the treatment of HIV-1 infection. The following points should be considered when initiating therapy with Lamivudine, Stavudine and Nevirapine Tablets:

- 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/mm<sup>3</sup> or in adult males with CD4+ cell counts greater than 400 cells/mm<sup>3</sup> 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; DOSAGE AND ADMINISTRATION).

## CONTRAINDICATIONS

Lamivudine, Stavudine and Nevirapine Tablets are contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the formulation.

## **WARNINGS**

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

### **Lamivudine and Stavudine**

#### ***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 and stavudine. 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 and stavudine 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 and/or stavudine 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).

Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness, see Neurologic Symptoms) might be indicative of the development of symptomatic hyperlactatemia or lactic acidosis syndrome.

### **Lamivudine**

**In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, Lamivudine should be used with caution. Treatment with Lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS).**

#### ***Important Differences Among Lamivudine-Containing Products:***

Lamivudine, Stavudine and Nevirapine Tablets contain a higher dose of the same active ingredient (lamivudine) than in EPIVIR-HBV tablets and oral Solution. EPIVIR-HBV was developed for patients with chronic hepatitis B. Lamivudine, Stavudine and Nevirapine Tablets should not be administered concomitantly with lamivudine, EPIVIR-HBV, RETROVIR, TRIZIVIR®, or EPZICOM.

#### ***Posttreatment Exacerbations of Hepatitis:***

In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis has developed

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

**Use With Interferon- and Ribavirin-Based Regimens:** In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. 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 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 EPIVIR should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of EPIVIR 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).

## Stavudine

### *Neurologic Symptoms:*

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including stavudine. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving stavudine therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, with a history of neuropathy, or in patients receiving other drugs that have been associated with neuropathy, including didanosine (see ADVERSE REACTIONS).

### *Pancreatitis:*

Fatal and nonfatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine with or without hydroxyurea in both treatment-naïve and treatment experienced patients, regardless of degree of



immunosuppression. The combination of stavudine and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of stavudine after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

## **Nevirapine**

### ***General:***

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

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

### ***Skin Reactions:***

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

Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue nevirapine and seek medical evaluation immediately (see PRECAUTIONS). Do not restart nevirapine 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 (4 mg/kg/day in pediatric patients), which has been shown to reduce the frequency of rash. If rash is observed during this lead-in period, dose escalation should not occur until the rash has resolved (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.

***Hepatic Events:***

Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with nevirapine. In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of patients who received nevirapine and 1.2% of patients in control groups.

The risk of symptomatic hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the nevirapine groups compared to controls through 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately half of the patients with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. 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; 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+ cell counts. In general, during the first 6 weeks of treatment, women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4+ cell counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4+ cell counts >250 cells/mm<sup>3</sup> had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4+ cell counts <250 cells/mm<sup>3</sup> (11% versus 0.9%). An increased risk was observed in men with CD4+ cell counts >400 cells/mm<sup>3</sup> (6.3% versus 1.2% for men with CD4+ cell counts <400 cells/mm<sup>3</sup>). However, all patients, regardless of gender, CD4 + cell count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4+ cell counts. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine is associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

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

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

### ***Resistance***

Nevirapine must not be used as a single agent to treat HIV-1 or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential for cross resistance. When discontinuing an antiretroviral regimen containing nevirapine, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than nevirapine are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop.

### ***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, Stavudine and Nevirapine:**

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

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

***Patients with Impaired Renal Function:*** Lamivudine, Stavudine and Nevirapine Combination Tablets are not recommended for patients with CrCL  $\leq 50$  mL/min or for patients on hemodialysis.

If dose adjustment is required, Lamivudine, Stavudine and Nevirapine Combination Tablets should not be administered because the tablet contains a fixed-dose combination of lamivudine, stavudine and nevirapine.

### **Lamivudine**

***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. Post-treatment exacerbations of hepatitis have also been reported (see WARNINGS).

### **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. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated. 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**).

It is not clear whether a dosing adjustment is needed for patients with mild to moderate hepatic impairment, because multiple dose pharmacokinetic data are not available for this population. However, patients with moderate hepatic impairment and ascites may be at risk of accumulating nevirapine in the systemic circulation. Caution should be exercised when nevirapine is administered to patients with moderate hepatic impairment. Nevirapine should not be administered to patients with severe 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-1 infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV-1 diseases.

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

## **INFORMATION FOR PATIENTS**

### **Lamivudine, Stavudine and Nevirapine Tablets:**

Lamivudine, Stavudine and Nevirapine Tablets are for oral ingestion only.

Patients should be advised of the importance of taking Lamivudine, Stavudine and Nevirapine Tablets on a regular dosing schedule and to avoid missing doses.

Patients should be informed that Lamivudine, Stavudine and Nevirapine Tablets are not a cure for HIV-1 infection, and that they may continue to acquire illnesses associated with HIV-1 infection, including opportunistic infections. They should be advised that this combination therapy has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.

Patients should be advised to remain under the care of a physician when using Lamivudine, Stavudine and Nevirapine Tablets.

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

Patients should be informed to take Lamivudine, Stavudine and Nevirapine Tablets every day as prescribed. Patients should not alter the dose without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose. Patients should be advised to report to their doctor the use of any other medications.

### **Lamivudine**

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

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. Patients should be advised that the long-term effects of lamivudine are unknown at this time.

Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis.

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.

### **Stavudine:**

Patients should be informed of the importance of early recognition of symptoms of symptomatic hyperlactatemia or lactic acidosis syndrome, which include unexplained weight loss, abdominal discomfort, nausea, vomiting, fatigue, dyspnea, and motor weakness. Patients in whom these symptoms develop should seek medical attention immediately. Discontinuation of stavudine therapy may be required.

Patients should be informed that an important toxicity of stavudine is peripheral neuropathy. Patients should be aware that peripheral neuropathy is manifested by numbness, tingling, or pain in hands or feet, and that these symptoms should be reported to their physicians. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients who have advanced HIV disease or a history of peripheral neuropathy, and that discontinuation of stavudine may be required if toxicity develops.

Caregivers of children receiving stavudine therapy should be instructed regarding detection and reporting of peripheral neuropathy.

**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/mm<sup>3</sup> in women and  $>400$  cells/mm<sup>3</sup> 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 nevirapine associated rash.

Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. Additionally, when oral contraceptives are used for hormonal regulation during nevirapine therapy, the therapeutic effect of the hormonal therapy should be monitored (see DRUG INTERACTIONS).

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

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

## **DRUG INTERACTIONS**

### **Lamivudine**

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

TMP 160 mg/SMX 800 mg once daily has been shown to increase lamivudine exposure (AUC) by 44% (see CLINICAL PHARMACOLOGY). No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat *Pneumocystis carinii pneumonia*. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

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

### **Stavudine**

(see also CLINICAL PHARMACOLOGY). Zidovudine competitively inhibits the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine should be avoided.

*In vitro* data indicate that the phosphorylation of stavudine is also inhibited at relevant concentrations by doxorubicin and ribavirin. The clinical significance of these *in vitro* interactions is unknown; therefore, concomitant use of stavudine with either of these drugs should be undertaken with caution.

### **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 co-administered with nevirapine.



The specific pharmacokinetic changes that occur with co-administration of nevirapine and other drugs are listed in CLINICAL PHARMACOLOGY, Table 3. Clinical comments about possible dosage modifications based on these pharmacokinetic changes are listed in Table 4. The data in Tables 3 and 4 are based on the results of drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

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 5. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in Table 5, 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.

<b>Table 4: Established Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies (See CLINICAL PHARMACOLOGY, Table 1 for Magnitude of Interaction)</b>		
Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
Clarithromycin	↓ Clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against <i>Mycobacterium avium-intracellulare</i> complex, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
	↑14-OH clarithromycin	
Efavirenz	↓ Efavirenz	Appropriate doses for this combination are not established.
Ethinyl estradiol	↓ Ethinyl estradiol	Oral contraceptives and other hormonal

and Norethindrone	↓ Norethindrone	methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.
Fluconazole	↑ Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine-associated adverse events.
Indinavir	↓ Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/Ritonavir	↓ Lopinavir	A dose increase of lopinavir/ritonavir to 533/133 mg twice daily with food is recommended in combination with nevirapine.
Methadone	↓ Methadone <sup>a</sup>	Methadone levels may be decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Nelfinavir	↓ Nelfinavir M8 Metabolite	The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
	↓ Nelfinavir Cmin	

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.

<sup>a</sup> Based on reports of narcotic withdrawal syndrome in patients treated with nevirapine and methadone concurrently, and evidence of decreased plasma concentrations of methadone

**Table 5: 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**

<b>Drug Class</b>	<b>Examples of Drugs</b>
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

<b>Examples of Drugs in Which Plasma Concentrations May Be Increased By Co-administration With Nevirapine</b>	
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Antithrombotics	Warfarin Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.
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### **CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**

**Lamivudine:** Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

**Stavudine:** In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses which produced exposures (AUC) 39 and 168 times, respectively, human exposure at the recommended clinical dose. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred at levels of exposure 250 (mice) and 732 (rats) times human exposure at the recommended clinical dose.

Stavudine was not mutagenic in the Ames, *E. coli* reverse mutation, or the CHO/HGPRT mammalian cell forward gene mutation assays, with and without metabolic activation. Stavudine produced positive results in the *in vitro* human lymphocyte clastogenesis and mouse fibroblast assays, and in the *in vivo* mouse micronucleus test. In the *in vitro* assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25 to 250 mcg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 mcg/mL, with and without metabolic activation). In the *in vivo* micronucleus assay, stavudine was clastogenic in bone marrow cells following oral stavudine administration to mice at dosages of 600 to 2000 mg/kg/day for 3 days. No evidence of impaired fertility was seen in rats with exposures (based on C<sub>max</sub>) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.

**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, stavudine and nevirapine are all classified under category C. There are no adequate and well-controlled studies in pregnant women. Lamivudine, Stavudine and Nevirapine Tablets should be used during pregnancy only if the potential benefits outweigh the potential risk.

**Lamivudine:** Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryo lethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times that in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

In 2 clinical studies conducted in South Africa, pharmacokinetic measurements were performed on samples from pregnant women who received lamivudine beginning at Week 38 of gestation (10 women who received 150 mg twice daily in combination with zidovudine and 10 who received lamivudine 300 mg twice daily without other antiretrovirals) or beginning at Week 36 of gestation (16 women who received lamivudine 150 mg twice daily in combination with zidovudine). These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the pregnant women were similar to those obtained following birth and in non-pregnant adults. Lamivudine concentrations were generally similar in maternal, neonatal, and cord serum samples. In a subset of subjects from whom amniotic fluid specimens were obtained following natural rupture of membranes, amniotic fluid concentrations of lamivudine ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily) and were typically greater than 2 times the maternal serum levels. See the ADVERSE REACTIONS section for the limited late-pregnancy safety information available from these studies. Lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

**Stavudine:** Reproduction studies have been performed in rats and rabbits with exposures (based on  $C_{max}$ ) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, while no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the human exposure, while survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of stavudine in pregnant women. Stavudine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues. Healthcare providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

**Nevirapine:** No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. In rats, a significant decrease in fetal body weight occurred at doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended human clinical dose.

The maternal and developmental no-observable-effect level dosages in rats and rabbits produced systemic exposures approximately equivalent to or approximately 50% higher, respectively, than those seen at the recommended daily human dose, based on AUC.

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV-1 infection. It is unclear if pregnancy augments the already increased risk observed in non-pregnant women (see WARNING).

## **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.** Additionally, because of the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving Lamivudine, Stavudine and Nevirapine Tablets.

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

is also excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

**Stavudine:** Studies in lactating rats demonstrated that stavudine is excreted in milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants.

**Nevirapine:** Nevirapine is excreted in breast milk.

#### **PEDIATRIC USE:**

Lamivudine, Stavudine and Nevirapine Tablets are recommended in pediatric patients >12 years of age and weighing  $\geq 50$  kg.

#### **GERIATRIC USE:**

Clinical studies of lamivudine, stavudine, and nevirapine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. 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. Because Lamivudine, Stavudine and Nevirapine Tablets are a fixed-dose combination, it should not be prescribed for patients who require dose reduction or have renal impairment with CrCL <50 mL/min.

#### **Stavudine**

Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

In a monotherapy Expanded Access Program for patients with advanced HIV infection, peripheral neuropathy or peripheral neuropathic symptoms were observed in 15/40 (38%) elderly patients receiving 40 mg twice daily and 8/51 (16%) elderly patients receiving 20 mg twice daily. Of the approximately 12,000 patients enrolled in the Expanded Access Program, peripheral neuropathy or peripheral neuropathic symptoms developed in 30% of patients receiving 40 mg twice daily and 25% of patients receiving 20 mg twice daily. Elderly patients should be closely monitored for signs and symptoms of peripheral neuropathy.

#### **ADVERSE REACTIONS**

Adverse events with lamivudine, stavudine, and nevirapine may be expected with the use of Lamivudine, Stavudine and Nevirapine Tablets. The adverse events reported with lamivudine, stavudine, and nevirapine are presented below.

#### **Lamivudine (*Adults*)**

**Clinical Trials in HIV:** Selected clinical adverse events with a  $\geq 5\%$  frequency during therapy with lamivudine 150 mg twice daily plus RETROVIR 200 mg 3 times daily compared with zidovudine are listed in Table 6.

<b>Table 6: Selected Clinical Adverse Events (<math>\geq 5\%</math> Frequency) in Four Controlled Clinical Trials</b>		
Adverse Event	Lamivudine 150 mg Twice Daily plus RETROVIR (n = 251)	RETROVIR * (n = 230)
<b>Body as a whole</b>		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
<b>Digestive</b>		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
<b>Nervous system</b>		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
<b>Respiratory</b>		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
<b>Skin</b>		
Skin rashes	9%	6%
<b>Musculoskeletal</b>		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

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

The types and frequencies of clinical adverse events reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar. The most common adverse events in both treatment groups were nausea, dizziness, fatigue and/or malaise, headache, dreams, insomnia and other sleep disorders, and skin rash.



Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received lamivudine in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and B3007.

Selected laboratory abnormalities observed during therapy are summarized in Table 7.

Test (Threshold Level)	24-Week Surrogate Endpoint Studies *		Clinical Endpoint Study *	
	Lamivudine plus RETROVIR	RETROVIR <sup>***</sup>	Lamivudine plus Current Therapy	Placebo plus Current Therapy <sup>****</sup>
Absolute neutrophil count (<750/mm <sup>3</sup> )	7.2%	5.4%	15%	13%
Hemoglobin (<8 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (<50,000/mm <sup>3</sup> )	0.4%	1.3%	2.8%	3.8%
ALT (>5 × ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5 × ULN)	1.7%	1.8%	4%	2.1%
Bilirubin (>2.5 × ULN)	0.8%	0.4%	ND	ND
Amylase (>2 × ULN)	4.2%	1.5%	2.2%	1.1%

\*The median duration on study was 12 months.

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

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

ULN = Upper limit of normal.

ND = Not done.

In small, uncontrolled studies in which pregnant women were given lamivudine alone or in combination with zidovudine beginning in the last few weeks of pregnancy (see PRECAUTIONS: Pregnancy), reported adverse events included anemia, urinary tract infections, and complications of labor and delivery. In post-marketing experience, liver function abnormalities and pancreatitis have been reported in women who received lamivudine in combination with other antiretroviral drugs during pregnancy. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared to other HIV-infected patients.

The frequencies of selected laboratory abnormalities reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens) were similar.

**Lamivudine in Patients with Chronic Hepatitis B:** Clinical trials in chronic hepatitis B used a lower dose of lamivudine (100 mg daily) than the dose used to treat HIV. The most frequent adverse events with lamivudine versus placebo were ear, nose, and throat infections (25% versus 21%); malaise and fatigue (24% versus 28%); and headache (21%

versus 21%), respectively. The most frequent laboratory abnormalities reported with lamivudine were elevated ALT, elevated serum lipase, elevated CPK, and post-treatment elevations of liver function tests. Emergence of HBV viral mutants during lamivudine treatment, associated with reduced drug susceptibility and diminished treatment response, was also reported (also see WARNINGS and PRECAUTIONS). Please see the complete prescribing information for EPIVIR-HBV tablets and Oral Solution for more information.

### ***Observed During Clinical Practice***

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

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

*Digestive:* Stomatitis.

*Endocrine and Metabolic:* Hyperglycemia.

*General:* 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 and PRECAUTIONS).

*Hypersensitivity:* Anaphylaxis, urticaria.

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

*Nervous:* Paresthesia, peripheral neuropathy.

*Respiratory:* Abnormal breath sounds/wheezing.

*Skin:* Alopecia, rash, pruritus.

### ***Stavudine (Adults)***

Fatal lactic acidosis has occurred in patients treated with stavudine in combination with other antiretroviral agents. Patients with suspected lactic acidosis should immediately suspend therapy with stavudine. Permanent discontinuation of stavudine should be considered for patients with confirmed lactic acidosis.

Stavudine therapy has rarely been associated with motor weakness, occurring predominantly in the setting of lactic acidosis. If motor weakness develops, stavudine should be discontinued.

Stavudine therapy has also been associated with peripheral sensory neuropathy, which can be severe, is dose related, and occurs more frequently in patients being treated with other drugs that have been associated with neuropathy (including didanosine), in patients with advanced HIV infection, or in patients who have previously experienced peripheral neuropathy.

Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases,

symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the dose (see DOSAGE AND ADMINISTRATION). If neuropathy recurs after resumption, permanent discontinuation of stavudine should be considered.

When stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. Pancreatitis, peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with stavudine in combination with didanosine and hydroxyurea (see WARNINGS and PRECAUTIONS).

Selected clinical adverse events that occurred in adult patients receiving stavudine in a controlled monotherapy study are provided in Table 8.

Adverse Events	Percent (%)	
	Stavudine <sup>b</sup> (40 mg twice daily) (n=412)	Zidovudine (200 mg 3 times daily) (n=402)
Headache	54	49
Diarrhea	50	44
Peripheral Neurologic Symptoms/Neuropathy	52	39
Rash	40	35
Nausea and Vomiting	39	44

<sup>a</sup> Any severity, regardless of relationship to study drug.

<sup>b</sup> Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

Pancreatitis was observed in 3 of the 412 adult patients who received stavudine in a controlled monotherapy study.

Selected clinical adverse events that occurred in antiretroviral-naïve adult patients receiving stavudine from two controlled combination studies are provided in Table 9.

	Percent (%)	
	Study	Study 2 <sup>b</sup>

Adverse Events	Stavudine + lamivudine + indinavir (n=100 <sup>c</sup> )	Zidovudine + lamivudine + indinavir (n=102)	Stavudine + didanosine + indinavir (n=102 <sup>c</sup> )	Zidovudine + lamivudine + indinavir (n=103)
Nausea	43	63	53	67
Diarrhea	34	16	45	39
Headache	25	26	46	37
Rash	18	13	30	18
Vomiting	18	33	30	35
Peripheral Neurologic Symptoms/Neuropathy	8	7	21	10

<sup>a</sup> Any severity, regardless of relationship to study regimen

<sup>b</sup> Study 2 compared two triple-combination regimens in 205 treatment-naïve patients. Patients received either stavudine (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir

<sup>c</sup> Duration of stavudine therapy = 48 weeks.

Pancreatitis resulting in death was observed in patients treated with stavudine plus didanosine, with or without hydroxyurea, in controlled clinical studies and in post-marketing reports.

Selected laboratory abnormalities reported in a controlled monotherapy study are provided in Table 10.

<b>Table 10: Selected Adult Laboratory Abnormalities in Monotherapy Study<sup>a,b</sup></b>		
	Percent (%)	
Parameter	Stavudine (40 mg twice daily) (n=412)	Zidovudine (200 mg 3 times daily) (n=402)
AST (SGOT) (>5 x ULN)	11	10
ALT (SGPT) (>5 x ULN)	13	11
Amylase ( $\geq 1.4$ x ULN)	14	13

<sup>a</sup> Data presented for patients for whom laboratory evaluations were performed

<sup>b</sup> Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

ULN = upper limit of normal.

Selected laboratory abnormalities reported in two-controlled combination studies are provided in Tables 11 and 12.

<b>Table 11: Selected Laboratory Abnormalities in Two Combination Therapy Studies (Grades 3-4)</b>	
	Percent (%)

Parameter	Study 1		Study 2	
	Stavudine + lamivudine+ indinavir (n=100)	Zidovudine+ lamivudine+ indinavir (n=102)	Stavudine + didanosine+ indinavir (n=102)	Zidovudine+ lamivudine+ indinavir (n=103)
Bilirubin (>2.6 x ULN)	7	6	16	8
AST (SGOT) (>5 x ULN)	5	2	7	7
ALT (SGPT) (>5 x ULN)	6	2	8	5
GGT (>5 x ULN)	2	2	5	2
Lipase (>2 x ULN)	6	3	5	5
Amylase (>2 x ULN)	4	<1	8	2

ULN = upper limit of normal.

**Table 12: Selected Laboratory Abnormalities in 2 Combination Therapy Studies (All Grades)**

Parameter	Percent (%)			
	Study 1		Study 2	
	Stavudine + lamivudine+ indinavir (n=100)	Zidovudine+ lamivudine+ indinavir (n=102)	Stavudine + didanosine+ indinavir (n=102)	Zidovudine+ lamivudine+ indinavir (n=103)
Total Bilirubin	65	60	68	55
AST (SGOT)	42	20	53	20
ALT (SGPT)	40	20	50	18
GGT	15	8	28	12
Lipase	27	12	26	19
Amylase	21	19	31	17

### ***Observed During Clinical Practice***

The following events have been identified during post-approval use of stavudine. 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 their seriousness, frequency of reporting, causal connection to stavudine, or a combination of these factors.

*Body as a Whole*- abdominal pain, allergic reaction, chills/fever, and redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

*Digestive Disorders*- anorexia.

*Exocrine Gland Disorders*- pancreatitis [including fatal cases (see WARNINGS)].

*Hematologic Disorders*- anemia, leukopenia, and thrombocytopenia.

*Liver*- symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see WARNINGS), hepatitis and liver failure.

*Musculoskeletal*- myalgia.

*Nervous System*- insomnia, severe motor weakness (most often reported in the setting of lactic acidosis, see WARNINGS).

### **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% (range 0% to 11%) of patients who received nevirapine and 1.2% of patients in control groups. Female gender and higher CD4+ cell counts (>250 cells/mm<sup>3</sup> in women and >400 cells/mm<sup>3</sup> 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. Coinfection 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.

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving nevirapine in placebo-controlled trials are shown in Table 13.

<b>Table 13: Percentage of Patients with Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials</b>				
	Trial 1090 <sup>1</sup>		Trials 1037, 1038, 1046 <sup>2</sup>	
	Nevirapine (n=1121)	Placebo (n=1128)	Nevirapine (n=253)	Placebo (n=203)
Median exposure (weeks)	58	52	28	28
Any adverse event	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0
Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2	0.5
Abdominal pain	0.1	0.4	2	0
Myalgia	0.2	0	1.2	2

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

<sup>2</sup> Background therapy included zidovudine and zidovudine plus didanosine; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count > 200 cells/mm<sup>3</sup>

**Laboratory Abnormalities:** Liver function test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls (Table 14). Asymptomatic elevations in GGT occur frequently but are not a contraindication to continue nevirapine therapy in the absence of elevations in other liver function tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing nevirapine and control regimens (see Table 14).

<b>Table 14: Percentage of Adult Patients with Laboratory Abnormalities</b>		
	Trial 1090 <sup>1</sup>	Trials 1037, 1038,

			1046 <sup>2</sup>	
	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%	4%
SGOT (AST) >250 U/L	3.7	2.5	7.6	1.5
Bilirubin >2.5 mg/dL	1.7	2.2	1.7	1.5
Hematology				
Hemoglobin <8 g/dL	3.2	4.1	0	0
Platelets <50,000/mm <sup>3</sup>	1.3	1	0.4	1.5
Neutrophils <750/mm <sup>3</sup>	13.3	13.5	3.6	1

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

<sup>2</sup>Background therapy included zidovudine and zidovudine plus didanosine; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count > 200 cells/mm<sup>3</sup>.

### ***Observed During Clinical Practice***

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

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

*Gastrointestinal:* vomiting

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

*Hematology:* anemia, eosinophilia, neutropenia

*Musculoskeletal:* arthralgia

*Neurologic:* paraesthesia

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

### **OVERDOSAGE**

**Lamivudine:** There is no known antidote for lamivudine. One case of an adult ingesting 6g of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in ACTG300. One case was a single dose of 7 mg/kg of lamivudine; the second case



involved use of 5 mg/kg of lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

**Stavudine:** Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by hemodialysis; the mean  $\pm$  SD hemodialysis clearance of stavudine is  $120 \pm 18$  mL/min. Whether stavudine is eliminated by peritoneal dialysis has not been studied.

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

## **DOSAGE AND ADMINISTRATION**

### ***Adults***

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

A 14 day lead-in period with once daily nevirapine has been associated with lower risks of rash. Therefore, the following regimen is recommended for the initial 14 days of dosing:

***For adult patients  $\geq 60$  kg:*** One Lamivudine, Stavudine and Nevirapine Tablet, 150 mg/40 mg/200 mg taken once per day followed by a daily oral dose of Lamivudine 150 mg and Stavudine 40 mg 12 hours later using an alternate formulation of these drugs.

***For patients  $< 60$  kg:*** One Lamivudine, Stavudine and Nevirapine Tablet, 150 mg/30 mg/200 mg taken once per day followed by a daily oral dose of Lamivudine 150 mg and Stavudine 30 mg 12 hours later.

#### **Maintenance:**

If the initial 14 days of nevirapine is tolerated without any hypersensitivity reactions (e.g. rash, liver function test abnormalities; see WARNINGS and PRECAUTIONS), the recommended maintenance oral dose is as follows:

***For patients  $\geq 60$  kg:*** One Lamivudine, Stavudine and Nevirapine Tablet, 150mg/40 mg /200 mg taken twice daily (at 12 hour intervals).

***For patients  $<60$  kg:*** One Lamivudine, Stavudine and Nevirapine Tablet, 150mg/30 mg/200 mg taken twice daily (at 12 hour intervals).

Lamivudine, Stavudine and Nevirapine Tablets should be taken at intervals of 12 hours under fasted conditions.

Because Lamivudine, Stavudine and Nevirapine Tablets are a fixed dose combination tablet, it should not be prescribed for patients requiring dosage adjustment or those experiencing dose-limiting adverse events.

### ***Pediatrics***

Lamivudine, Stavudine and Nevirapine Tablets 150 mg/30 mg/200mg are recommended for pediatric patients > 12 years of age and weighing  $\geq 50$  kg. Lamivudine, Stavudine and Nevirapine Tablets 150 mg/40 mg/200 mg are recommended for pediatric patients > 12 years of age and weighing  $\geq 60$  kg.

### ***Geriatrics***

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

### **Monitoring**

Patients should be monitored for the development of peripheral neuropathy, which is usually characterised by numbness, tingling, or pain in the feet or hands. If these symptoms develop, therapy with Lamivudine, Stavudine and Nevirapine Tablets should be interrupted. Symptoms may resolve if therapy is withdrawn promptly. Some patients may experience a temporary worsening of symptoms following discontinuation of therapy.

Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment. 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 the treatment. In some cases, hepatic injury has progressed despite discontinuation of treatment.

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

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

*Hepatic impairment:* Caution should be exercised when Lamivudine, Stavudine and Nevirapine Tablets are administered to patients with moderate hepatic impairment. Lamivudine, Stavudine and Nevirapine Tablets should not be administered to patients with severe hepatic impairment.

*Renal impairment:* Lamivudine, Stavudine and Nevirapine Tablets are not recommended for patients with creatinine clearance  $\leq 50$  ml/min.

Note: Zidovudine in combination with Lamivudine, Nevirapine and Stavudine Tablets is not recommended (see **PRECAUTIONS: Drug Interactions**). Didanosine in combination with Lamivudine, Nevirapine and Stavudine Combination Tablets is not recommended (see **Warnings and PRECAUTIONS**).

#### **HOW SUPPLIED**

Lamivudine, Stavudine and Nevirapine Tablets 150 mg/30 mg/200 mg are light pink and Lamivudine, Stavudine and Nevirapine Tablets 150 mg/40 mg/200 mg are light yellow colored. Both strength tablets are circular and flat bevel-edged tablets with SLN engraved on one side plain on other side. Tablets are supplied in HDPE Container of 60.

**Storage:** Lamivudine, Stavudine and Nevirapine Tablets should not be stored above 25° C (77° F). Protect from light. Keep in a well-closed container. Store in a safe place out of reach of children.

**Manufactured by:**  
**STRIDES ARCOLAB LIMITED,**  
**BANGALORE,**  
**INDIA.**

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

## MEDICATION GUIDE

### **Lamivudine, Stavudine and Nevirapine Tablets**

(Lamivudine 150 mg, Stavudine 30 mg and Nevirapine 200 mg)

(Lamivudine 150 mg, Stavudine 40 mg and Nevirapine 200 mg)

**Generic name:** Lamivudine/Stavudine/Nevirapine (lah MIH vue deen/STA vue deen / na VAIR a peen) tablets.

Read this Medication Guide before you start taking **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** and each time you get a refill because there may be new information. This information does not take the place of talking with your doctor. You and your doctor should discuss **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** when you start taking your medicine and at regular checkups. You should stay under a doctor's care while using **LAMIVUDINE, STAVUDINE AND NEVIRAPINE COMBINATION 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, STAVUDINE AND NEVIRAPINE TABLETS?**

Your doctor will tell you how many **Lamivudine, Nevirapine and Stavudine Tablets** to take and how often to take them. Your doctor will determine your dose based on your body weight, kidney and liver function.

Take **Lamivudine, Nevirapine and Stavudine Tablets** exactly as instructed. Do not take more than the doctor told you to. Check the label carefully for how much to take and how often to take.

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

**Patients taking LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS may develop severe liver disease or skin reactions that can cause death.** The risk of these reactions is greatest during the first 18 weeks of treatment, but these reactions also can occur later.

### ***Liver Reactions***

Any patient can experience liver problems while taking LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS. However, women and patients who have higher CD4 counts when they begin LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS treatment have a greater chance of developing liver damage. Women with CD4 counts higher than 250 cells/mm<sup>3</sup> are at the greatest risk of these events. If you are a woman with CD4>250 cells/mm<sup>3</sup> or a man with CD4>400 cells/mm<sup>3</sup> you should not begin taking LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS unless you and your doctor have decided that the benefit of doing so outweighs the risk. Liver problems are often accompanied by a rash.

Patients starting LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS with abnormal liver function tests and patients with hepatitis B or C have a greater chance of developing further increases in liver function tests after starting LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS and throughout therapy.

**In rare cases liver problems have led to liver failure and can lead to a liver transplant or death. Therefore, if you develop any of the following symptoms of liver problems, stop taking LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS and call your doctor right away:**

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

Your doctor should check you and do blood tests often to check your liver function during the first 18 weeks of therapy. Checks for liver problems should continue regularly during treatment with LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS.

**Worsening of hepatitis B virus infection. Patients with HBV infection, who take LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS and then stop it, may get “flare-ups” of their hepatitis. “Flare-up” is when the disease suddenly returns in a worse way than before. If you have HBV infection, your doctor should closely monitor your liver function for several months after stopping LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS. You may need to take anti-HBV medications.**

**Use with interferon- and ribavirin-based regimens.** Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C who are taking anti-HIV medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** as well as interferon with or without ribavirin and you experience side effects, be sure to tell your doctor.

### ***Skin Reactions***

Skin rash is the most common side effect of **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**. Most rashes occur in the first 6 weeks of treatment. In a small number of patients, **rash can be serious and result in death**. Therefore, **if you develop a rash with any of the following symptoms stop using LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS and call your doctor right away:**

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

**If your doctor tells you to stop treatment with LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS because you have experienced the serious liver or skin reactions described above, never take LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS again.**

### ***Lactic Acidosis***

**LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** can cause a condition called lactic acidosis, together with an enlarged liver. Symptoms of lactic acidosis may include:

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

If you notice these symptoms or if your medical condition suddenly changes, stop taking **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS and call your doctor right away**. Lactic acidosis is a medical emergency that must be treated in a hospital.

This rare, but serious side effect occurs more often in women (including pregnant women), overweight patients, and those who have been taking nucleoside medicines for a

very long time. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

### ***Pancreatitis***

**LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS can cause pancreatitis**, a dangerous inflammation of the pancreas. It may cause death. **Tell your doctor right away if you develop stomach pain, nausea, or vomiting. These can be signs of pancreatitis.** Let your doctor know if you have ever had pancreatitis, regularly drink alcoholic beverages, or have gallstones. Pancreatitis occurs more often in patients with these conditions. It is also more likely in people with advanced HIV disease, but can occur at any disease stage.

These are not all the side effects of **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**. (See the section "What are the possible side effects of **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS?**" for more information.) Tell your doctor if you have any side effects from **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**.

### **What are LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS and what are they used for?**

**LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** is a combination of three drugs- Lamivudine, Stavudine and Nevirapine, which are also available as separate drugs and are commonly used to treat Human Immunodeficiency Virus (HIV) infection.

Each tablet of **LAMIVUDINE, STAVUDINE AND NEVIRAPINE 150 mg/30 mg/200 mg** contains 150 mg lamivudine, 30 mg stavudine and 200 mg nevirapine.

Each tablet of **LAMIVUDINE, STAVUDINE AND NEVIRAPINE 150 mg/40 mg/200 mg** contains 150 mg lamivudine, 40 mg stavudine and 200 mg nevirapine.

- **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** are used for treatment of HIV infection in adults. **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** reduce the amount of HIV virus in the body and increase CD4 cell counts. CD4 cells are a type of white blood cell, which plays an important role in maintaining a healthy immune system to help fight infection. Response to treatment with **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** varies between patients. It is very important that you stay under the care of your doctor. Your doctor may want you to have blood tests or other medical evaluations during treatment with this medication to monitor effectiveness and side effects.

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

### **Who should not take LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS?**

#### **Do not take LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS if:**

- You are allergic to any of the ingredients in **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**. Your doctor or pharmacist can tell you about the inactive ingredients.
- Do not restart **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** if you have experienced and recovered from serious side effects such as serious liver or skin reactions, blood problems, or lactic acidosis that happened when you took **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** or **any of the individual active ingredients**.
- Do not take **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** if you take certain medicines. (See “Can I take other medicines with **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS?**” for a list of medicines.)
- Do not take these medicines if you are not infected with HIV.

Lamivudine, Stavudine and Nevirapine Tablets, 150 mg/30 mg/200 mg and 150 mg/40 mg/200 mg, are not recommended in children less than 12 years of age and weighing less than 50 kg.

### **What should I tell my doctor before taking LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS?**

Before you start taking **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**, tell your doctor about all of your medical conditions, including if you:

- have liver disease or have had hepatitis
- have kidney disease or are undergoing dialysis
- have skin conditions, such as a rash



- are pregnant, planning to become pregnant, or are breast feeding
- You may not be able to take this combination, or you may require or special monitoring during treatment if you have any of the conditions listed above.
- We do not know if **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** will harm your unborn baby. You and your doctor will need to decide if **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** are right for you.
- If you are breast feeding, **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** can be passed to your baby in your breast milk. It is not known if they could harm your baby.

### **How should I take LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS?**

**Your doctor will recommend that you take Lamivudine, Nevirapine and Stavudine Tablets twice daily only if you have tolerated 14 days of treatment with pills containing Nevirapine 200 mg taken once daily (along with pills containing Lamivudine and Stavudine taken twice daily). The 14 day period of once daily nevirapine reduces the risk of getting a severe rash.**

#### ***Adults***

**Take** Lamivudine, Stavudine and Nevirapine Tablets twice daily on an empty stomach.

#### ***Pediatrics***

Lamivudine, Stavudine and Nevirapine Tablets are recommended in children older than 12 years of age and weighing more than or equal to 50 kg. Tablets should be taken twice daily on an empty stomach.

Take all doses of **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**. Missing doses can make the virus harder to treat. If you forget to take a dose of **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**, take the missed dose as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Instead, follow your regular dosing schedule by taking the next dose at its regular time. Do not let your **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** run out.

If you stop taking **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** for more than 7 days, do not start taking lamivudine, stavudine, nevirapine tablets without asking your doctor. If you suspect that you have taken too much **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**, contact your local poison control center or emergency room right away.

### **Can I take other medicines with LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS?**

Since **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** is a combination of lamivudine, stavudine and nevirapine, do not take medicines, which already contain these three drugs.

- **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** may change the effect of other medicines, and other medicines can change the effect of **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**. Tell your doctors and pharmacists about **all** medicines you take, including non-prescription medicines, vitamins and herbal supplements.
- Do **not** take ketoconazole or rifampin with **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**
- Tell your doctor if you take clarithromycin, fluconazole, methadone, or rifabutin. **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** may not be right for you, or you may need careful monitoring.
- **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** should not be taken with zalcitabine, high doses of co-trimoxazole, or injections of ganciclovir or foscarnet, as lamivudine, one of the active substances in **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** may interact with these.
- **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** should also not be taken with zidovudine and doxorubicin as stavudine, one of the active substances in **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** may reduce the action of these medicinal products.
- It is recommended that you not take products containing St. John's wort, which can reduce the amount of **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** in your body.
- If you take birth control pills, you should not rely on them to prevent pregnancy. They may not work if you take **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**. Talk with your doctor about other types of birth control that you can use.

### **What should I avoid while taking LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS?**

Avoid doing things that can spread HIV infection, as **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** does 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?**

**LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** can cause serious liver damage, skin reactions, pancreatitis and lactic acidosis that may result in 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, STAVUDINE AND NEVIRAPINE TABLETS**?" at the beginning of this Medication Guide.)

**LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS can cause peripheral neuropathy**, a nerve disorder of the hands and feet. If not recognized promptly, this disorder may worsen. **Tell your doctor right away** if you have continuing numbness, tingling, burning, or pain in the feet and/or hands.

Other common side effects of **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** include nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain, myalgias and blood disorders.

Combination antiretroviral therapy with lamivudine and stavudine may cause raised lactic acid and sugar in the blood, hyperlipemia (increased fats in the blood) and resistance to insulin.

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.

This list of side effects is not complete. Ask your doctor or pharmacist for more information

### **How do I store LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS?**

Store at room temperature, between 15°C-25°C (59°F-77°F). Do not take the medicine after the expiry date on the packaging. Keep out of the reach and sight of children.

### **General information about LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** for a condition for which it was not prescribed. Do not give **LAMIVUDINE, STAVUDINE AND NEVIRAPINE TABLETS** to other people, even if they have the same condition you have. It may harm them. This Medication Guide summarizes the most important information about **LAMIVUDINE, STAVUDINE AND NEVIRAPINE**

**TABLETS.** If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information that is written for health professionals.

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