

Stavudine and Lamivudine Tablets Co-Packaged With Nevirapine Tablets Rx only

WARNING

SEVERE, LIFE-THREATENING, AND IN SOME CASES FATAL HEPATOTOXICITY, PARTICULARLY IN THE FIRST 18 WEEKS, HAS BEEN REPORTED IN PATIENTS TREATED WITH NEVIRAPINE TABLETS. IN SOME CASES, PATIENTS PRESENTED WITH NON-SPECIFIC PRODROMAL SIGNS OR SYMPTOMS OF HEPATITIS AND PROGRESSED TO HEPATIC FAILURE. THESE EVENTS ARE OFTEN ASSOCIATED WITH RASH. FEMALE GENDER AND HIGHER CD4 COUNTS AT INITIATION OF THERAPY PLACE PATIENTS AT INCREASED RISK; WOMEN WITH CD4 COUNTS >250 CELLS/mm³, INCLUDING PREGNANT WOMEN RECEIVING NEVIRAPINE IN COMBINATION WITH OTHER ANTIRETROVIRALS FOR THE TREATMENT OF HIV INFECTION, ARE AT THE GREATEST RISK. HOWEVER, HEPATOTOXICITY ASSOCIATED WITH NEVIRAPINE USE CAN OCCUR IN BOTH GENDERS, ALL CD4 COUNTS AND AT ANY TIME DURING TREATMENT. PATIENTS WITH SIGNS OR SYMPTOMS OF HEPATITIS, OR WITH INCREASED TRANSAMINASES COMBINED WITH RASH OR OTHER SYSTEMIC SYMPTOMS, MUST DISCONTINUE NEVIRAPINE AND SEEK MEDICAL EVALUATION IMMEDIATELY (SEE WARNINGS).

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

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).

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

FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF STAVUDINE AND DIDANOSINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF STAVUDINE AND DIDANOSINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS: PREGNANCY).

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-NAIVE AND TREATMENT EXPERIENCED - PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (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

Stavudine (d4T) is a synthetic thymidine nucleoside analogue, active against the human immunodeficiency virus (HIV).

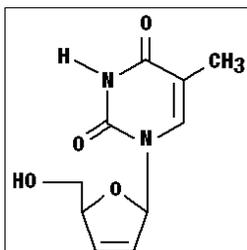
Lamivudine (3TC) is a synthetic nucleoside analogue with activity against HIV-1 and HBV.

Nevirapine (NVP) non-nucleoside reverse transcriptase inhibitor with activity against Human Immunodeficiency Virus Type 1 (HIV-1).

Stavudine and lamivudine fixed dose combination and nevirapine tablets are for oral administration. Each uncoated tablet contains the active ingredients 40 mg of stavudine and 150 mg of lamivudine fixed dose combination, the inactive ingredients microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, ferric oxide red, povidone, magnesium stearate and purified water. Each uncoated Nevirapine tablet contains active

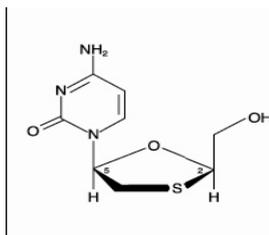
ingredient nevirapine 200 mg and the inactive ingredients microcrystalline cellulose, lactose, croscarmellose sodium, povidone, colloidal anhydrous silica, purified talc, magnesium stearate and purified water.

Stavudine: The chemical name for stavudine is 2', 3'-didehydro-3'-deoxythymidine. Stavudine has the following structural formula:



Stavudine is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.2. The solubility of stavudine 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.

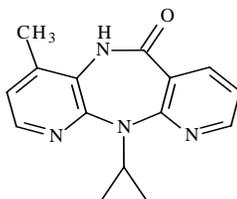
Lamivudine: The chemical name of lamivudine is (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-) 2', 3'-dideoxy, 3'-thiacytidine. It has a molecular formula of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



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

Nevirapine: The chemical name of nevirapine is 11-cyclopropyl-5, 11-dihydro-4-methyl-6H-dipyrido (3,2-b:2',3'-e)(1,4) diazepin-6-one. Nevirapine is structurally a member of the dipyridodiazepinone chemical class of compounds.

Nevirapine has a molecular weight of 266.30 and the molecular formula of $C_{15}H_{14}N_4O$. Nevirapine has the following structural formula:



Nevirapine is a white to off-white crystalline powder.

MICROBIOLOGY

MECHANISM OF ACTION

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 μ M) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases β and γ and markedly reduces the synthesis of mitochondrial DNA.

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 nucleotide analogue into viral DNA. 3TC -TP is a weak inhibitor of mammalian DNA polymerases α , β and γ .

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

Antiviral Activity

Stavudine: The *in vitro* 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% (EC₅₀) ranged from 0.009 to 4 µM against laboratory and clinical isolates of HIV-1. *In vitro*, stavudine exhibited additive to antagonistic activity in combination with zidovudine. Stavudine in combination with either abacavir, didanosine, tenofovir, or zalcitabine exhibited additive to synergistic anti-HIV-1 activity. Ribavirin, at the 9-45 µM concentrations tested, reduced the anti-HIV-1 activity of stavudine by 2.5- to 5-fold. The relationship between *in vitro* susceptibility of HIV-1 to stavudine and the inhibition of HIV-1 replication in humans has not been established.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC₅₀ values (50% effective concentrations) were in the range of 0.003 to 15 µM (1 µM = 0.23 mcg/mL). HIV from therapy-naïve subjects with no mutations associated with resistance gave median EC₅₀ values of 0.426 µM (range: 0.200 to 2.007 µM) from Virco (n = 93 baseline samples from COLA40263) and 2.35 µM (1.44 to 4.08 µM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC₅₀ values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 µM, and against HIV-2 isolates from 0.003 to 0.120 µM in peripheral blood mononuclear cells. Ribavirin (50 µM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Nevirapine: The *in vitro* antiviral activity of nevirapine was measured in peripheral blood mononuclear cells, monocyte derived macrophages and lymphoblastoid cell lines. EC₅₀ values (50% effective concentration) ranged from 10-100 nM against laboratory and clinical isolates of HIV-1. In cell culture, nevirapine demonstrated additive to synergistic activity against HIV-1 in drug combination regimens with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine (ddl), lamivudine (3TC), stavudine (d4T) and zidovudine (ZDV), and the protease inhibitors indinavir and saquinavir.

RESISTANCE

Stavudine: HIV-1 isolates with reduced susceptibility to stavudine have been selected *in vitro* (strain-specific) and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV-1 isolates from 61 patients receiving prolonged (6-29 months) stavudine monotherapy showed that post-therapy isolates from four patients exhibited IC₅₀ 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. The genetic basis for stavudine susceptibility changes has not been identified.

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected 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 (M 184 V/I).

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 mono therapy 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 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).

Nevirapine: HIV-1 isolates with reduced susceptibility (100-250-fold) to nevirapine emerge *in vitro*. Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance *in vitro* was not altered when selection included nevirapine in combination with several other NNRTIs. Genotypic analysis of isolates from antiretroviral naïve virologic failure patients (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine (study 2NN) for 48 weeks showed that isolates from 8/25 and 23/46 patients, respectively, contained one or more of the following NNRTI resistance-associated mutations: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

Phenotypic and genotypic changes in HIV-1 isolates from treatment naïve patients receiving either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase I/II trials over 1 to ≥ 12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine *in vitro*. One or more of the RT mutations K103N, V106A, V108I, Y181C, Y188C and G190A were detected in HIV-1 isolates from some patients as early as 2 weeks after therapy initiation. By week eight of nevirapine mono therapy, 100% of the patients tested (n=24) had HIV-1 isolates with a >100-fold decrease in susceptibility to nevirapine *in vitro* compared to baseline, and had one or more of the nevirapine-associated RT resistance mutations. 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 mutations: 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 (ddl) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

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 mutations (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 ddl 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 and Stavudine combination tablets, and Nevirapine tablets was similar to that from Epivir[®] tablets, Zerit[®] capsules, and Viramune[®] tablets respectively, when administered to healthy volunteers in the fasted state.

ABSORPTION AND BIOAVAILABILITY

Stavudine: Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as tablet or capsules or solution. Steady-state pharmacokinetic parameters of Stavudine in HIV-infected adults are shown in Table 1.

Table 1: Steady-State Pharmacokinetic Parameters of Stavudine in HIV Infected Adults

Parameter	Stavudine 40 mg BID Mean ± SD (n=8)
AUC (ng·h/mL) ^a	2568 ± 454
C _{max} (ng/mL)	536 ± 146
C _{min} (ng/mL)	8 ± 9

^a from 0 to 24 hours.

AUC = area under the curve over 24 hours.

C_{max} = maximum plasma concentration.

C_{min} = trough or minimum plasma concentration.

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

Nevirapine: Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 µg/mL (7.5 µM) were attained by 4 hours following a single 200 mg dose.

Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5 ± 1.9 µg/mL (17 ± 7 µM), (n = 242) were attained at 400 mg/day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox[®] 30 ml), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate study in HIV-1 infected patients (n=6), nevirapine steady-state systemic exposure (AUC_τ) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without food, antacid or didanosine.

DISTRIBUTION

Stavudine: Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 µg/mL. Stavudine distributes equally between red blood cells and plasma. Volume of distribution is shown in Table 2.

Table 2: Pharmacokinetic Parameters of Stavudine in HIV-Infected Adults: Bioavailability, Distribution, and Clearance

Parameter	Mean ± SD	n
Oral bioavailability (%)	86.4 ± 18.2	25
Volume of distribution (L) ^a	46 ± 21	44
Total body clearance (mL/min) ^a	594 ± 164	44
Apparent oral clearance (mL/min) ^b	560 ± 182 ^c	113
Renal clearance (mL/min) ^a	237 ± 98	39
Elimination half-life, IV dose (h) ^a	1.15 ± 0.35	44
Elimination half-life, oral dose (h) ^b	1.6 ± 0.23	8
Urinary recovery of stavudine (% of dose) ^{a,d}	42 ± 14	39

^a following 1-hour IV infusion.

^b following single oral dose.

^c assuming a body weight of 70 kg.

^d over 12-24 hours.

Lamivudine: The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine

distributes into extra vascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. Binding of lamivudine to human plasma proteins is low (<36%). In vitro studies showed that, over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Nevirapine: Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (V_{dss}) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is also found in breast milk (See **PRECAUTIONS, Nursing Mothers**). Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 $\mu\text{g/mL}$. Nevirapine concentrations in human cerebrospinal fluid ($n=6$) were 45% ($\pm 5\%$) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

METABOLISM / ELIMINATION

Stavudine: The metabolic fate of stavudine has not been elucidated in humans. 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. The remaining 60% of the drug is presumably eliminated by endogenous pathways.

Lamivudine: 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.

The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL/min (mean \pm SD). In 20 HIV-infected patients given a single IV dose, renal clearance was 280.4 ± 75.2 mL/min (mean \pm SD), representing $71\% \pm 16\%$ (mean \pm SD) of total clearance of lamivudine. In most single-dose studies in HIV-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean \pm SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

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

Nevirapine is an inducer of hepatic cytochrome p450 (CYP) metabolic enzymes 3A4 and 2B6. Nevirapine induces CYP3A4 and CYP2B6 by approximately 20-25%, as indicated by erythromycin breath test results and urine metabolites. Auto induction of CYP3A4 and CYP2B6 mediated metabolism leads to an approximately 1.5 to 2 fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to four weeks of dosing with 200-400 mg/day. Auto induction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma, from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

Effect of food on Absorption of Lamivudine/Stavudine Tablets Co-Packaged with Nevirapine.

The effect of food on the rate and extent of absorption of Lamivudine/Stavudine combination tablets co-packaged with Nevirapine tablets is not known, so Stavudine/Lamivudine tablets and Nevirapine Tablets should be taken under fasting conditions.

Special Populations:

Impaired Renal Function:

Stavudine/Lamivudine combination tablets co-packaged with Nevirapine tablets is not recommended for patients with impaired renal function (see DOSAGE and ADMINISTRATION: PRECAUTIONS)

Impaired Hepatic Function:

Stavudine/Lamivudine combination tablets co-packaged with Nevirapine tablets is not recommended for patients with impaired hepatic function.

Pregnancy: See PRECAUTIONS: Pregnancy

Stavudine/Lamivudine combination tablets co-packaged with 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 Tablets Co-packaged with Nevirapine Tablets are recommended in pediatric patients >12 years and $\geq 60\text{kg}$.

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

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

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

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±7.7 mL/kg/hr in females vs. 19.9±3.9 mL/kg/hr in males after single dose) or plasma concentrations following either single- or multiple-dose administration(s).

RACE

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

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

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

DRUG INTERACTIONS

Stavudine:

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

Doxorubicin: In vitro data indicate that the phosphorylation of stavudine is inhibited at relevant concentrations by doxorubicin.

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

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; 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 3 and 4 summarize the effects on AUC and C_{max}, with a 95% confidence interval (CI) when available, following coadministration of stavudine with didanosine, lamivudine, and nelfinavir. No clinically significant pharmacokinetic interactions were observed.

Table 3: Results of Drug Interaction Studies with Stavudine: Effects of Coadministered Drug on Stavudine Plasma AUC and C_{max} Values

Drug	Stavudine Dosage	n ^a	AUC of Stavudine (95% CI)	C _{max} 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%.

^a HIV-infected patients.

Table 4: Results of Drug Interaction Studies with Stavudine: Effects of Stavudine on Coadministered Drug Plasma AUC and C_{max} Values

Drug	Stavudine Dosage	n ^a	AUC of Coadministered Drug (95% CI)	C _{max} of Coadministered 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%.

^a HIV-infected patients.

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

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% ± 23% (mean ± SD) in lamivudine AUC_∞, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine.

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.

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 μM, a concentration that is unlikely to be achieved in patients as the therapeutic range is <25 μM. Therefore, nevirapine may have minimal inhibitory effect on other substrates of CYP3A4. Nevirapine does not appear to affect the plasma concentrations of drugs that are substrates of other CYP450 enzyme systems, such as 1A2, 2D6, 2A6, 2E1, 2C9 or 2C19.

Table 5 contains results of drug interaction studies performed with nevirapine and other drugs likely to be co-administered. The effects of nevirapine on the AUC, C_{max}, and C_{min} of co-administered drugs are summarized. To measure the full potential pharmacokinetic interaction effect following induction, patients on the concomitant drug at steady state were administered 28 days of nevirapine (200 mg QD for 14 days followed by 200 mg BID for 14 days) followed by a steady state reassessment of the concomitant drug.

Table 5: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Nevirapine (All interaction studies were conducted in HIV-1 positive patients)

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of Nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters(90%CI)		
				AUC	C _{max}	C _{min}
Antiretrovirals				AUC	C _{max}	C _{min}
Didanosine	100-150 mg BID	200 mg QD x 14 days 200 mg BID x 14 days	18	↔	↔	§
Efavirenz ^a	600 mg QD	200 mg QD x 14 days 400 mg QD x 14 days	17	↓28 (↓34 to ↓14)	↓12 (↓23 to ↑1)	↓32 (↓35 to ↓19)
Indinavir ^a	800 mg q8H	200 mg QD x 14 days 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir ^{a, b}	300/75 mg/m ² (lopinavir/ ritonavir) ^b	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15 ^c	↓14 (↓36 to ↑16)	↓22 (↓44 to ↑9)	↓55 (↓75 to ↓9)
Lopinavir ^a	400/100 mg BID (lopinavir/ ritonavir)	200 mg QD x 14 days; 200 mg BID > 1 year	22, 19 ^c	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Nelfinavir ^a	750 mg TID	200 mg QD x 14 days 200 mg BID x 14 days	23	↔	↔	↓32 (↓50 to ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)
Ritonavir	600 mg BID	200 mg QD x 14 days 200 mg BID x 14 days	18	↔	↔	↔
Saquinavir ^a	600 mg TID	200 mg QD x 14 days 200 mg BID x 21 days	23	↓38 (↓47 to ↓11)	↓32 (↓44 to ↓6)	§
Stavudine	30-40 mg BID	200 mg QD x 14 days 200 mg BID x 14 days	22	↔	↔	§
Zalcitabine	0.125-0.25 mg TID	200 mg QD x 14 days 200 mg BID x 14 days	6	↔	↔	§
Zidovudine	100-200 mg TID	200 mg QD x 14 days 200 mg BID x 14 days	11	↓28 (↓40 to ↓4)	↓30 (↓51 to ↑14)	§
Clarithromycin ^a	500 mg BID	200 mg QD x 14 days 200 mg BID x 14 days	15	↓31 (↓38 to ↓24)	↓23 (↓31 to ↓14)	↓57 (↓70 to ↓36)
Metabolite 14-OH clarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	↔

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of Nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters(90%CI)		
Ethinyl estradiol ^a and Norethindrone ^a	0.035 mg (as Ortho-Novum® 1/35)	200 mg QD x 14 days 200mg BID x 14 days	10	↓20 (↓33 to ↓3)	↔	§
	1 mg (as Ortho-Novum® 1/35)			↓19 (↓30 to ↓7)	↓16 (↓27 to ↓3)	§
Fluconazole	200 mg QD	200 mg QD x 14days 200 mg BID x 14 days	19	↔	↔	↔
Ketoconazole ^a	400 mg QD	200 mg QD x 14 days 200 mg BID x 14 days	21	↓72 (↓80 to ↓60)	↓44 (↓58 to ↓27)	§
Rifabutin ^a	150 or 300 mg QD	200 mg QD x 14 days 200 mg BID x 14 days	19	↑17 (↓2 to ↑40)	↑28 (↑9 to ↑51)	↔
Metabolite 25-O- desacetyl rifabutin				↑24 (↓16 to ↑84)	↑29 (↓2 to ↑68)	↑22 (↓14 to ↑74)
Rifampin ^a	600 mg QD	200 mg QD x 14 days 200 mg BID x 14 days	14	↑11 (↓4 to ↑28)	↔	§

§ = Cmin below detectable level of the assay ↑ = Increase, ↓ = Decrease, ↔ = No Effect

^a For information regarding clinical recommendations

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

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

INDICATIONS AND USAGE

Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets are indicated for the treatment of HIV-1 infection once patients have demonstrated adequate tolerability to an initial two weeks of treatment with nevirapine 200 mg taken once daily in combination with lamivudine and stavudine twice daily.. The following points should be considered when initiating therapy with Stavudine and Lamivudine Tablets Co-Packaged with 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/mm³ or in adult males with CD4+ cell counts greater than 400 cells/mm³ unless the benefit outweighs the risk (see WARNINGS).

- The 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash (see WARNINGS; DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

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

WARNINGS

Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets should not be administered concomitantly with formulations containing any of the three drugs. The complete prescribing information for all agents being considered for use with Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets should be consulted.

Stavudine and Lamivudine :

Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and lamivudine. 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 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.

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.

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

Post-treatment Exacerbations of Hepatitis

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

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 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.

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

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

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

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

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

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

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).

Skin Reactions: Severe, life-threatening skin reactions, including fatal cases, have been reported with nevirapine treatment, 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. Nevirapine should not be restarted following severe skin rash 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. Patients should be monitored closely if isolated rash of any severity occurs.

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

In a clinical trial, concomitant prednisone use was associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine therapy. Therefore, use of prednisone to prevent nevirapine-associated rash is not recommended.

Resistance: 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

Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets:

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 stavudine, lamivudine and nevirapine therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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

Patients with Impaired Renal Function: Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets are not recommended for patients with CrCL ≤ 50 mL/min or for patients on hemodialysis.

If dose adjustment is required, Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets should not be administered.

Lamivudine:

Impaired Renal Function: Reduction of the dosage of lamivudine is recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Patients With HIV and Hepatitis B Virus Coinfection: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response.

Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-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. No adjustment in nevirapine dosing is required in patients with CrCL ≥ 20 mL/min. 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 infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

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

INFORMATION FOR PATIENTS

Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets

Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets are for oral ingestion only.

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

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

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 dose modification and/or discontinuation of stavudine may be required if toxicity develops.

Patients should be informed that 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. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Patients treated with this combination should be closely monitored for symptoms of pancreatitis. An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with stavudine in combination with didanosine and hydroxyurea. This combination should be avoided.

Lamivudine:

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

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 skin reactions should be instructed to 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. Patients with signs and symptoms of hepatitis should seek medical evaluation immediately. If nevirapine is discontinued due to hepatitis, it should not be restarted. Patients should be advised that co-infection with hepatitis B or C and/or increased liver function tests at the start of antiretroviral therapy are associated with a greater risk of hepatic events with nevirapine. Women and patients with increased CD4+ cell count (>250 cells/mm³ in women and >400 cells/mm³ in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Patients should be advised that co-infection with hepatitis B or C and/or increased liver function tests at the start of antiretroviral therapy are associated with a greater risk of hepatic events with nevirapine (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 severe rash or hypersensitivity reactions should discontinue nevirapine 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.

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

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

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 43% (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.

Stavudine

(see also **CLINICAL PHARMACOLOGY-Drug Interactions**). 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 5. Clinical comments about possible dosage modifications based on these pharmacokinetic changes are listed in Table 6. The data in Tables 5 and 6 are based on the results of drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are listed in Table 7. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in Table 7, additional clinical monitoring may be warranted when co-administering these drugs.

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

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
Clarithromycin	↓ Clarithromycin ↑14-OH clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against <i>Mycobacterium avium</i> -intracellular complex, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.

Drug	Interaction	Notes
Efavirenz	↓Efavirenz	Appropriate doses for this combination are not established.
Ethinyl estradiol and Norethindrone	↓Ethinyl estradiol ↓Norethindrone	Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.
Fluconazole	↑Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine-associated adverse events.
Indinavir	↓Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Ketoconazole	↓Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/Ritonavir	↓Lopinavir	A dose increase of lopinavir/ritonavir to 533/133 mg twice daily with food is recommended in combination with nevirapine.
Methadone	↓Methadone ^a	Methadone levels may be decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Nelfinavir	↓Nelfinavir M8 Metabolite ↓Nelfinavir Cmin	The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high inter subject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampin	↓Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine containing regimen may use rifabutin instead.
Saquinavir	↓Saquinavir	Appropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.

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

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

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

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 µg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 µg/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_{max}) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.

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.

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.

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

There are no adequate and well-controlled studies in pregnant women. Stavudine/Lamivudine Tablets co-pacaged with Nevirapine Tablets should be used during pregnancy only if the potential benefits outweigh the potential risk.

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 (see WARNINGS: Lactic Acidosis/Severe Hepatomegaly with Steatosis). The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk. Health care providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

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.

Nevirapine

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

The maternal and developmental no-observable-effect level dosages in rats and rabbits produced systemic exposures approximately equivalent to or approximately 50% higher, respectively, than those seen at the recommended daily human dose, based on AUC. There are no adequate and well-controlled studies in pregnant women. Nevirapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets.

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. Because of both the potential for HIV transmission and the potential

for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving stavudine.

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. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving lamivudine.

Nevirapine: Nevirapine is excreted in breast milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving nevirapine.

PEDIATRIC USE

Stavudine and Lamivudine Tablet Co-Packaged with Nevirapine Tablet are recommended in pediatric patients >12 years and ≥ 60kg.

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. Stavudine and Lamivudine Tablets Co-packaged with Nevirapine Tablets 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 Stavudine and Lamivudine Tablets Co-packaged with Nevirapine Tablets. The adverse events reported with lamivudine, stavudine, and nevirapine are presented below.

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 neurotoxic drug therapy, 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. 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. 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 (stavudine) in a controlled monotherapy study are provided in Table 8.

Table 8: Selected Clinical Adverse Events in Study AI455 019^a (Monotherapy)

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

^a Any severity, regardless of relationship to study drug.

^b 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 naive adult patients receiving stavudine from two controlled combination studies are provided in Table 9.

Table 9 Selected Clinical Adverse Events in START 1 and START 2^b Studies (Combination Therapy)

Adverse Events	Percent (%)			
	START 1 Stavudine + lamivudine + indinavir (n=100 ^c)	zidovudine + lamivudine + indinavir (n=102)	START 2b Stavudine + didanosine + indinavir (n= 102 ^c)	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

^a Any severity, regardless of relationship to study regimen.

^b START 2 compared two triple-combination regimens in 205 treatment-naïve patients. Patients received stavudine (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir.

^c 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 postmarketing reports.

Selected laboratory abnormalities reported in a controlled monotherapy study (Study AI455-019) are provided in Table 10.

Table 10: Selected Adult Laboratory Abnormalities in Study AI455 019^{a,b}

Parameter	Percent (%)	
	Stavudine (40 mg twice daily) (n=412)	Zidovudine (200 mg 3 times daily) (n=402)
AST (SGOT) (>5.0 x ULN)	11	10
ALT (SGPT) (>5.0 x ULN)	13	11
Amylase (≥1.4 x ULN)	14	13

^a Data presented for patients for whom laboratory evaluations were performed.

^b 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 Table 11.

Table 11: Selected Laboratory Abnormalities in Two Combination Therapy Studies (Grades 3-4)				
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)
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.

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

Hematologic Disorders - anemia, leukopenia, and thrombocytopenia.

Liver - lactic acidosis and hepatic steatosis, hepatitis and liver failure.

Musculoskeletal - myalgia.

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

Lamivudine:

Adults

Selected clinical adverse events with a ≥5% frequency during therapy with lamivudine 150 mg twice daily plus zidovudine 200 mg 3 times daily compared with zidovudine are listed in Table 12.

Table 12: Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical Trials (A3001, A3002, B3001, B3002)

Adverse Event	Lamivudine 150 mg Twice Daily Plus zidovudine (n = 251)	zidovudine * (n = 230)
Body as a Whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous System		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

* Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

The types and frequencies of clinical adverse events reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily 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, NUCA3002, NUC3002, and B3007.

Selected laboratory abnormalities observed during therapy are summarized in Table 13.

Table 13: Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study (B3007)

Test (Threshold Level)	24-Week Surrogate Endpoint Studies*		Clinical Endpoint Study*	
	Lamivudine plus Zidovudine	Zidovudine †	Lamivudine plus Current Therapy	Placebo plus Current Therapy ‡

Absolute neutrophil count (<750/mm ³)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (>5.0 x ULN)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST(>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (<2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

* The median duration on study was 12 months.

† Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

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

ULN = Upper limit of normal

ND = Not done

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, 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 in EPV20001 and EPV400001) 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 posttreatment 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).

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.

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, post treatment exacerbation of hepatitis B.

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, rash, pruritus.

Nevirapine

The most serious adverse reactions associated with nevirapine are clinical hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Clinical 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, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction (see WARNINGS).

Adults

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

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

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

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving nevirapine in placebo-controlled trials are shown in Table 14.

Table 14: Percentage of Patients with Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials

	Trial 1090 ¹		Trials 1037, 1038, 1046 ²	
	Nevirapine (n=1121)	Placebo (n=1128)	Nevirapine (n=253)	Placebo(n=203)
Median exposure	58	52	28	28

(weeks)				
Any adverse event	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0
Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2.0	0.5
Abdominal pain	0.1	0.4	2.0	0
Myalgia	0.2	0	1.2	2.0

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

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

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

Table 15: Percentage of adult patients with laboratory abnormalities

Laboratory abnormalities	Trial 1090 ¹		Trials 1037, 1038, 1046 ²	
	Nevirapine (n=1121)	Placebo (n=1128)	Nevirapine (n=253)	Placebo(n=203)
Blood chemistry				
SGPT (ALT) >250 U/L	5.3%	4.4%	14.0%	4.0%
SGOT (AST) >250 U/L	3.7	2.5	7.6	1.5
Bilirubin >2.5 mg/dL	1.7	2.2	1.7	1.5
Hematology				
Hemoglobin <8.0 g/dL	3.2	4.1	0	0
Platelets <50,000/mm ³	1.3	1.0	0.4	1.5
Neutrophils <750/mm ³	13.3	13.5	3.6	1.0

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

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

Observed During Clinical Practice: The following events have been reported with the use of nevirapine in clinical practice

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

Gastrointestinal: vomiting

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

Hematology: anemia, eosinophilia, 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

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 ± SD hemodialysis clearance of stavudine is 120 ± 18 mL/min. Whether stavudine is eliminated by peritoneal dialysis has not been studied.

Lamivudine

There is no known antidote for lamivudine. One case of an adult ingesting 6 g 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.

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

If the initial 14 days of once daily nevirapine (in combination with twice daily stavudine and lamivudine) is tolerated without any hypersensitivity reactions (e.g. rash, liver function test abnormalities; see **WARNINGS** and **PRECAUTIONS**), the recommended maintenance oral dose of Lamivudine/Stavudine

Tablets co-packaged with Nevirapine Tablets is as follows:

Adults weighing 60 ≥ kg

One Stavudine/Lamivudine Tablet and one Nevirapine Tablet (40mg/150mg/200mg) taken twice daily (at 12 hour intervals) under fasted state.

Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets should not be prescribed for patients weighing less than 60 kg, requiring dosage adjustment or experiencing dose-limiting adverse events.

Pediatrics

Stavudine/Lamivudine Tablets copackaged with Nevirapine Tablets (40mg/150mg/200mg) are recommended under fasting conditions for pediatric patients >12 years of age and patients weighing ≥60 kgs.

Geriatrics

Although no specific dosage alterations are recommended, caution should be exercised when Lamivudine/ Stavudine Tablets 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 Tablets 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 Tablets 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 Tablets and Nevirapine Tablets can cause hepatitis. If clinical hepatitis occurs, Lamivudine/Stavudine Tablets and Nevirapine Tablets should be discontinued. Do not restart Lamivudine/ Stavudine Tablets and Nevirapine Tablets after recovery (see WARNINGS).

Patients who interrupt Lamivudine/Stavudine Tablets and Nevirapine Tablets dosing for more than 7 days should restart with the recommended 14 day lead-in dosing of Nevirapine Tablets once daily (administered with twice daily stavudine and lamivudine) After 14 days, maintenance dosing with Lamivudine/Stavudine Tablets co-packaged with Nevirapine Tablets daily may be resumed.

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

Renal impairment: Lamivudine/Stavudine Tablets copackaged with Nevirapine Tablets are not recommended for patients with creatinine clearance ≤ 50 ml/min.

HOW SUPPLIED

Stavudine 40mg and lamivudine 150mg fixed dose combination tablet, is a light pink to pink colored, circular, flat bevel edged tablets with LS40 engraved on one side and plain on other side. 60 tablets are packed in a 50ml HDPE container closed by a snap cap with a tear-off tamper-evident strip.

NEVIRAPINE Tablets, 200 mg, is a white oval shaped tablet with N200 engraved on one side and plain on other side. 60 tablets are packed in a 50ml HDPE container closed by a snap cap with a tear-off tamper-evident strip.

One container of each is co-packaged in a printed paperboard carton.

STORAGE

Stavudine and Lamivudine:

Store below 30°C. Protect from light. Keep all medicines away from children.

Nevirapine:

Store below 30°C. Protect from light. Keep all medicines away from children

STRIDES ARCOLAB LIMITED, Bangalore- India.

MEDICATION GUIDE

Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets

Generic Name: stavudine (STA vue deen) and lamivudine (la MIH vue deen) along with nevirapine (na VAIR a peen)

Read this Medication Guide before you start taking the combination of stavudine + lamivudine, co-packed along with nevirapine, 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 regarding these medicines when you start taking it and at regular checkups. You should stay under a doctor's care while using these medications. 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 this Co-Package?

- Fixed dose combination tablet of stavudine and lamivudine can cause the following side effects: This medication should not be taken together with another medication that contains a combination of lamivudine and zidovudine (Combivir). Before taking Lamivudine, tell your doctor if you have kidney disease, liver disease, a pancreas disorder, or problems with your muscles. Call your doctor at once if you have liver problems while you are using Lamivudine. Symptoms to watch for include stomach pain, nausea and vomiting, low fever, loss of appetite, dark urine, clay-colored stools, or jaundice (yellowing of the skin or eyes).
- Lamivudine can lower the blood cells in your body that help you fight infections. This can make it easier for you to bleed from an injury or get sick from being around others who are ill. To be sure your blood cells do not get too low, your blood will need to be tested on a regular basis. It is important that you not miss any scheduled visits to your doctor.
- If you have hepatitis B you may develop liver symptoms after you stop taking Lamivudine, even months after stopping. Your doctor may want to check your liver function on a regular basis for several months after you stop using this medication. Do not miss any scheduled visits.
- Lactic acidosis (the build up of lactic acid in the body) and severe liver problems, including fatal cases, have been reported with the use of reverse transcriptase inhibitors, such as stavudine, lamivudine, alone or in combination. Contact your doctor immediately if you experience nausea, vomiting, or unusual or unexpected stomach discomfort; weakness and tiredness; shortness of breath; weakness in the arms and legs; yellowing of the skin or eyes; or pain in the upper stomach area. These may be early symptoms of lactic acidosis or liver problems. Call your doctor at once if you have any of these symptoms, even if they are only mild. Early signs of lactic acidosis generally get worse over time and this condition can be fatal.
- Serious cases of pancreatitis (inflammation of the pancreas) have been reported with the use of Stavudine or lamivudine. Notify your doctor immediately if you develop symptoms of pancreatitis including nausea, vomiting, diarrhea, abdominal pain and/or fever.
- Avoid alcohol while taking lamivudine. Alcohol may increase the risk of damage to the pancreas and/ or liver.
- Follow your doctor's instructions with respect to high-risk activities such as unprotected sex and the sharing of needles. Lamivudine does not reduce the risk of transmitting the

HIV or hepatitis B virus to others and you can still transmit the virus to others during therapy with this medication.

- The most common side effect from stavudine therapy is peripheral neuropathy, which may cause loss of feeling, numbness, tingling, or pain in a part of the body. Approximately 20% of patients taking stavudine will experience peripheral neuropathy. Contact your doctor if you experience any of these side effects.

Nevirapine tablets can cause the following side effects:

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

Liver Reactions

Any patient can experience liver problems while taking nevirapine. However, women and patients who have higher CD4 counts when they begin treatment with nevirapine have a greater chance of developing liver damage. Women with CD4 counts higher than 250 cells/mm³ are at the greatest risk of these events. If you are a woman with CD4>250 cells/mm³ or a man with CD4>400 cells/mm³ you should not begin taking nevirapine unless you and your doctor have decided that the benefit of doing so outweighs the risk. Liver problems are often accompanied by a rash. Patients with abnormal liver function tests and patients with hepatitis B or C have a greater chance of developing further increases in liver function tests after starting nevirapine and throughout therapy.

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

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

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

Skin Reactions

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

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

If your doctor tells you to stop treatment with nevirapine because you have experienced the serious liver or skin reactions described above, never take again until your doctor advises you. These are not all the side effects of lamivudine, stavudine and nevirapine. (See the section "What are the possible side effects?" for more information.) Tell your doctor if you have any side effects from these medications.

What are Stavudine and Lamivudine Tablets and Nevirapine Tablets

Stavudine, lamivudine and nevirapine are antiviral medications. Stavudine and lamivudine are in a category of HIV medicines called reverse transcriptase inhibitors. They inhibit the reproduction of viruses in the body.

Stavudine, lamivudine, and nevirapine are used to treat the human immunodeficiency virus (HIV), which causes the acquired immunodeficiency syndrome (AIDS). It is not a cure for HIV or AIDS.

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

The medicine in this Co-package can reduce viral load and increase the number of CD4 cells ("T cells"). CD4 cells are a type of immune helper cell in the blood. Nevirapine may not have these effects in every patient. These medications do not cure HIV or AIDS. People taking this medication may still get infections common in people with HIV (opportunistic infections). Therefore, it is very important that you stay under the care of your doctor.

Who should not take Stavudine and Lamivudine Tablets Co-Packaged with Nevirapine Tablets?

- Do not take if you are allergic to stavudine, lamivudine or nevirapine or any of its ingredients. Your doctor or pharmacist can tell you about the inactive ingredients.
- Do not restart the medication after you recover from side effects of these medications such as lactic acidosis, serious liver or skin reactions until your doctor advises.
- Do not take these medications if you take certain medicines. (See "Can I take other medicines?" for a list of medicines.)
- Do not take nevirapine if you are not infected with HIV.

What should I tell my doctor before taking these medications?

Before taking the combination of stavudine and lamivudine co-packed with nevirapine, tell your doctor if you

- have kidney disease or are undergoing dialysis
 - have liver disease or have had hepatitis
 - have bone marrow suppression
 - weight less than 110 pounds (50 kg).
 - have skin conditions, such as a rash or
 - are pregnant, planning to become pregnant, or are breast feeding
 - have pancreatitis
 - history of peripheral neuropathy (numbness and tingling sensation)
-
- You may not be able to take this combination, if you have any of the conditions listed above.
 - If you are pregnant. Stavudine and lamivudine is in the FDA pregnancy category C. This means that it is not known whether the combination of stavudine and lamivudine will be harmful to an unborn baby. It is very important to treat HIV/AIDS during pregnancy to reduce the risk of infecting the baby. Talk to your doctor about your treatment options. Tell your doctor if you are pregnant or plan to become pregnant during treatment. HIV can be passed

to the baby if the mother is not properly treated during pregnancy. Tell your doctor if you are pregnant or plan to become pregnant during treatment. Take all of your HIV medicines as directed to control your infection while you are pregnant.

- If you are breast feeding, because it is not known whether this combination of stavudine, lamivudine and nevirapine passes into breast milk and what affect it may have on a nursing baby. To prevent transmission of the virus to uninfected babies, it is recommended that HIV-positive mothers not breast-feed. Even if your baby is born without HIV, you may still pass the virus to the baby in your breast milk. Talk to your doctor about breast-feeding if you are taking lamivudine and stavudine.

How should I take these medications?

Take the medications in this co-package exactly as directed by your doctor. Do not take the medication in larger amounts, or take it for longer than recommended by your doctor. If you do not understand these directions, ask your pharmacist, nurse, or doctor to explain them to you.

- Take each dose with a full glass of water.
- These medications should be taken without food.
- The usual dose of the fixed dose combination of stavudine and lamivudine (both the medications are present in one single tablet) for adult is 1 tablet taken twice a day. The usual dose of nevirapine for adults is one tablet daily for the first 14 days followed by one tablet twice daily. Starting with one dose a day lowers the chance of rash, which could be serious. Therefore, it is important to strictly follow the once daily dose for the first 14 days. Follow your doctor's instructions.
- It is important to take these medications regularly to get the most benefit.
- HIV/AIDS is usually treated with a combination of different drugs. To best treat your condition, use all of your medications as directed by your doctor. Be sure to read the medication guide or patient instructions provided with each of your medications. Do not change your doses or medication schedule without advice from your doctor. Every person with HIV or AIDS should remain under the care of a doctor.
- If you have hepatitis B you may develop liver symptoms after you stop taking this medication, even months after stopping. Your doctor may want to check your liver function at regular visits for several months after you stop using Lamivudine/Stavudine combination tablets. Do not miss any scheduled visits.
- Treatment of HIV/AIDS almost always requires the use of two or more drugs. If you need to stop taking one of the medicines you are taking for HIV, you should stop all of them until you can talk to your doctor.
- Your doctor may want you to have blood tests or other medical evaluations during treatment with this medication to monitor progress and side effects.
- Store these medications at room temperature away from moisture and heat.

What happens if I miss a dose?

- Do not miss a dose. If you forget then, take the missed dose as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and take only the next regularly scheduled dose. **Do not** take a double dose of this medication unless your doctor directs otherwise.
- If you miss too many doses, then contact your doctor.
- If you suspect that you have taken too much of these medications, contact your local poison control center or emergency room right away.

What happens if I overdose?

Seek emergency medical attention.

Symptoms of overdose include liver damage (yellowing of the skin or eyes, nausea, abdominal pain or discomfort, unusual bleeding or bruising, severe fatigue) and numbness, tingling, or pain in a part of the body.

What should I avoid while taking these medications?

- Follow your doctor's instructions with respect to high-risk activities such as unprotected sex and the sharing of needles. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood. These medications do not cure HIV or AIDS and you can still transmit the virus to others during therapy with this medication.
- This medication should not be taken together with another medication that contains lamivudine
- Avoid contact with people who have colds, the flu, or other contagious illnesses. Contact your doctor immediately if you develop signs of infection.
- Avoid having unprotected sex or sharing needles, razors, or toothbrushes. Taking this medication will not prevent you from passing HIV to other people. Talk with your doctor about safe methods of preventing HIV transmission during sex, such as using a condom and spermicide. Sharing drug or medicine needles is never safe, even for a healthy person.
- Avoid alcohol. Alcohol may increase the risk of damage to the pancreas and/or liver.
- 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?

(See "What is the most important information I should know about this Co-Package?" at the beginning of this Medication Guide.)

Stavudine and lamivudine combination tablet can cause

- Lactic acidosis (build up of lactic acid in the blood) and severe liver problems, including fatal cases, have been reported with the use of reverse transcriptase inhibitors, alone or in combination. Contact your doctor immediately if you experience nausea, vomiting, or unusual or unexpected stomach discomfort; weakness and tiredness; shortness of breath; weakness in the arms and legs; yellowing of the skin or eyes; or pain in the upper stomach area. These may be early symptoms of lactic acidosis or liver problems.
- Serious, even fatal, cases of pancreatitis (inflammation of the pancreas) have been reported with the use of some reverse transcriptase inhibitors. Notify your doctor immediately if you develop symptoms of pancreatitis including nausea, vomiting, diarrhea, abdominal pain, and/or fever.
- The most common side effect of stavudine is peripheral neuropathy, which may cause loss of feeling, numbness, tingling, or pain in a part of the body. Approximately 20% of patients taking stavudine will experience peripheral neuropathy. Contact your doctor if you experience any of these side effects.
- If you experience any of the following serious side effects, stop taking this combination of stavudine and lamivudine and seek emergency medical attention or notify your doctor immediately:
 - an allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives);
 - muscle pain or weakness; or
 - peripheral neuropathy (nerve damage), which may cause numbness, tingling, or pain.
 - trouble breathing, fast or uneven heart rate, nausea, vomiting, stomach pain, numbness or cold feeling;
 - fever, chills, body aches, flu symptoms;
 - easy bruising or bleeding, unusual weakness, pale skin;

- nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes);
- sudden and severe stomach pain with nausea, vomiting, fever, chills, and rapid pulse; or
- white patches or sores inside your mouth or on your lips.

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

- mild nausea, vomiting, diarrhea, or decreased appetite;
- a headache;
- dizziness;
- insomnia; or
- redistribution of body fat (loss of fat from the arms, legs, and face and increased fat around the neck, breast, and trunk);
- rash;
- fever or chill.

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

Nevirapine can cause

- Serious liver damage and skin reactions that can cause death. Any patient can experience such side effects, but some patients are more at risk than others.
- Other common side effects of nevirapine include nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain, and myalgia. This list of side effects is not complete. Ask your doctor or pharmacist for more information.
- Changes in body fat have also been seen in some patients taking antiretroviral therapy. The changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

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

Can I take other medicines?

Before taking these medications, tell your doctor if you are using any of the following drugs:

- interferon-alfa (Roferon, Intron, Rebetron);
- trimethoprim (Bactrim, Proloprim, Septra, Trimpex); or
- ribavirin (Rebetol, Ribasphere, Copegus Virazole).

There may be other drugs not listed that can affect the medicines in this co-package. Tell your doctor about all the prescription and over-the-counter medications you use. This includes vitamins, minerals, herbal products, and drugs prescribed by other doctors. Do not start using a new medication without telling your doctor.

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

- Do not take Nizoral[®] (ketoconazole) or Rifadin[®] /Rifamate[®] /Rifater[®] (rifampin) with nevirapine. Tell your doctor if you take Biaxin[®] (clarithromycin), Diflucan[®] (fluconazole), methadone, or

Mycobutin[®] (rifabutin). Nevirapine may not be right for you, or you may need careful monitoring.

- It is recommended that you do not take products containing St. John's wort, which can reduce the amount of nevirapine in your body.
- If you take birth control pills, you should not rely on them to prevent pregnancy. They may not work if you take nevirapine. Talk with your doctor about other types of birth control that you can use.

How do I store these medications?

Store below 30°C. Protect from light. Keep all medicines away from children. Throw away medicines that are no longer needed or out-of-date.

Where can I get more information?

Your pharmacist has more information about lamivudine, stavudine and nevirapine written for health professionals that you may read.

General information

This medication is sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use these medications for a condition for which it was not prescribed. Do not give these medications 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 stavudine and lamivudine combination tablet and nevirapine tablet. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about these medications.

What are the ingredients in lamivudine/stavudine tablets co-packaged with nevirapine tablets?

Active ingredients: lamivudine, stavudine and nevirapine.

Inactive ingredients:

Stavudine/lamivudine tablets: The inactive ingredients in the stavudine/lamivudine tablet includes microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, ferric oxide red, povidone, magnesium stearate and purified water.

Nevirapine Tablets: The inactive ingredients in the nevirapine tablet include microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, colloidal anhydrous silica, purified talc, purified water and magnesium stearate.

For additional information contact:
Strides Arcolab Ltd
Bilekahalli, Opp. IIMB

Bannerghatta Road,
Bangalore – 560076
India

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