HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lamivudine Nevirapine and Zidovudine tablets for oral suspension safely and effectively. See full prescribing information for Lamivudine Nevirapine and Zidovudine tablets for oral suspension.

Lamivudine Nevirapine and Zidovudine tablets for oral suspension

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY, SKIN REACTIONS, EXACERBATIONS OF HEPATITIS B, MYOPATHY, RISK OF HEMATOLOGICAL TOXICITY and LACTIC ACIDOCIS.

See full prescribing information for complete boxed warning.

- Fatal and non-fatal hepatotoxicity (5.1)
- Fatal and non-fatal skin reactions (5.2)
- Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV-l and have discontinued Lamivudine, one component of Lamivudine, Nevirapine and Zidovudine. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.3)
- Symptomatic myopathy associated with prolonged use of zidovudine-containing products (5.4)
- Hematologic toxicity including neutropenia and anemia have been associated with the use of zidovudine, one of the components of Lamivudine, Nevirapine and Zidovudine Tablets (5.10)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including zidovudine. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur (5.11)

Discontinue nevirapine-containing products immediately if experiencing:

- Signs or symptoms of hepatitis (5.1)
- Increased transaminases combined with rash or other systemic symptoms (5.1)
- Severe skin or hypersensitivity reactions (5.2)
- Any rash with systemic symptoms (5.2)

Monitoring during the first 18 weeks of therapy is essential. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events (5)

----------INDICATIONS AND USAGE----------

- Lamivudine, Nevirapine and Zidovudine, a combination of two nucleoside analog HIV-1 reverse transcriptase inhibitors (lamivudine and zidouvine) and one non-nucleoside analogue reverse transcriptase inhibitor (nevirapine), is indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in children weighing 5 to 25 kg.

Important considerations with the use of nevirapine-containing products:

- The 14-day lead-in period with different formulation of the drugs in this combination tablet must be strictly followed; it has been demonstrated to reduce the frequency of rash (2.3, 5.2)

----------DOSAGE AND ADMINISTRATION----------

- Pediatrics: Dosage should be based on body weight. 2.1
- Lamivudine, nevirapine and zidovudine, a fixed-dose product, should not be prescribed for pediatric patients who are less than 3 months of age and weigh less than 5 kg, or patients requiring dosage adjustment, such as those with renal or hepatic impairment, or patients experiencing dose-limiting adverse reactions. (2.3)
- If any patient experiences rash during the 14-day lead-in period, which requires different formulations of nevirapine, do not increase dose or switch to the combination tablet until the rash has resolved. Do not continue the lead-in dosing regimen beyond 28 days
- If dosing is interrupted for greater than 7 days, restart 14-day once-daily lead in dosing of nevirapine, which requires different formulations of the drugs in this combination tablet.

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets for oral suspension; Scored 30 mg lamivudine, 50 mg nevirapine and 60 mg zidovudine (3)

----------CONTRAINDICATIONS----------

Lamivudine, Nevirapine and Zidovudine is contraindicated in patients with:

- Previously demonstrated clinical significant hypersensitivity (e.g., anaphylaxis, Stevens-Johnson syndrome (4)
- Moderate to Severe (Child-Pugh class B or C respectively) hepatic impairment (4, 5.10, 8.7)
- For use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens, an unapproved use (4, 5.10)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Fatal and non-fatal hepatotoxicity has been reported. Monitor liver function tests before and during therapy. Permanently discontinue nevirapine-containing products if clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur. Do not restart nevirapine-containing products after recovery. (5.1)
- Rash: Fatal and non-fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions, have been reported. Permanently discontinue nevirapine-containing products if severe skin reactions or hypersensitivity reactions occur. Check transaminase immediately for all patients who develop a rash in the first 18 weeks of treatment. (5.2)
- See boxed warning for information about the following: hematologic toxicity, symptomatic myopathy, lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B. (5.10, 5.4, 5.11. 5.3)
- Lamivudine, Nevirapine and Zidovudine should not be administered with other lamivudine- , zidovudine-, or nevirapine-containing products or emtricitabine-containing products. (5.9)
- Hepatic decompensation, some fatal, has occurred in HIV -1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with/without ribavirin. Discontinue Lamivudine, Nevirapine and Zidovudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.5)
- Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Co-administration of ribavirin and zidovudine is not advised. (5.5)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.6)
- Immune reconstitution syndrome (5.7) and redistribution/accumulation of body fat (5.8) have been reported in patients treated with combination antiretroviral therapy.

----------ADVERSE REACTIONS----------

- The most commonly reported adverse reactions (incidence greater than or equal to 15%) in adult and pediatric HIV-1 clinical studies of combination lamivudine and zidovudine were headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea, and cough. (6.1, 6.2)
- The most common adverse reaction of nevirapine is rash. In adults the incidence of rash is 14.8% vs. 5.9% with placebo, with Grade 3/4 rash occurring in 1.5% of patients (6.1)
- In pediatric patients the incidence of rash (all causality) due to nevirapine was 21% (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Strides Inc. at (732)-839-1601 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Concomitant use with the following drugs should be avoided: stavudine (7.1) and doxorubicin (7.2).
- Bone marrow suppressive/cytotoxic agents: May increase the hematologic toxicity of zidovudine. (7.3)
- Co-administration of nevirapine-containing products can alter the concentrations of other drugs and other drugs may alter the concentration of Nevirapine. The potential for drug interactions must be considered prior to and during therapy (5.13, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Monitor patients with hepatic fibrosis or cirrhosis carefully for evidence of drug induced toxicity. Do not administer nevirapine to patients with Child Pugh B or C (5.1, 8.7).

For 17 PATIENT COUNSELING INFORMATION See Medication Guide.

Revised: November 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY, SKIN REACTIONS, EXACERBATIONS OF HEPATITIS B, MYOPATHY, RISK OF HEMATOLOGICAL TOXICITY and LACTIC ACIDOSIS

Hepatotoxicity: Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with Nevirapine-containing products. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher $CD4^+$ cell counts at initiation of therapy place patients at increased risk; women with $CD4^+$ cell counts greater than 250 cells/mm^3, including pregnant women receiving Nevirapine in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk. However, hepatotoxicity associated with Nevirapine use can occur in both genders, all $CD4^+$ cell counts and at any time during treatment. Hepatic failure has also been reported in patients without HIV taking Nevirapine containing products for post-exposure prophylaxis (PEP). Use of Nevirapine containing products for occupational and non-occupational PEP is contraindicated *[see Contraindications (4)]*. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue Nevirapine- containing products and seek medical evaluation immediately *[see Warnings and Precautions (5.1)]*.

Skin Reactions: Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with Nevirapine-containing products. 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-containing products and seek medical evaluation immediately. Transaminase levels should be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. The 14-day lead-in period with nevirapine once-daily dosing has been observed to decrease the incidence of rash and must be followed *[see Warnings and Precautions (5.2)]*.

Monitoring: Patients must be monitored intensively during the first 18 weeks of therapy with Nevirapine-containing products to detect potentially life-threatening hepatotoxicity or skin reactions. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart Nevirapine-containing products following clinical hepatitis, or transaminase elevations combined with rash or other systemic symptoms, or following skin rash or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment.

Exacerbations of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-l and have discontinued lamivudine-containing products. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue lamivudine-containing and are co-infected with HIV-l and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.3)]*.

Myopathy: Prolonged use of zidovudine-containing products has been associated with symptomatic myopathy *[see Warnings and Precautions (5.4)]*.

Hematologic Toxicity: Zidovudine-containing products have been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced human immunodeficiency virus (HIV-1) disease *[see Warnings and Precautions (5.10)*].

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicities occur *[see Warnings and Precautions (5.11)*].

1. INDICATION AND USAGE

Lamivudine, Nevirapine and Zidovudine is indicated alone or in combination with other antiretrovirals for the treatment of HIV-1 in children weighing 5 to 25 kg.

This fixed combination replaces the three components (Lamivudine, Nevirapine and Zidovudine) used separately in similar dosages. Treatment must be started with different formulations of Lamivudine, Nevirapine and Zidovudine for the first 14 days, until the patient is stable on the twice daily Nevirapine maintenance dose and adequate tolerability of Lamivudine, Nevirapine and Zidovudine has been demonstrated.

Additional important information regarding the use of nevirapine-containing products for the treatment of HIV-1 infection:

- The 14-day lead-in period with once-daily dosing of nevirapine must be strictly followed; it has been demonstrated to reduce the frequency of rash *[see Dosage and Administration (2.1) and Warnings and Precautions (5.2)]*.
- If rash persists beyond the 14-day lead-in period for nevirapine, do not dose escalate to twice daily. The once-daily dosing regimen should not be continued beyond 28 days, at which point an alternative regimen should be sought.

2. DOSAGE AND ADMINISTRATION

2.1 Pediatric Patients (at least 3 months of age and weighing greater than or equal to 5 kg)

Lamivudine, nevirapine and zidovudine (containing 30 mg of lamivudine, 50 mg of nevirapine and 60 mg of zidovudine) cannot be administered for the first 2-week lead-in period of once-daily nevirapine administration (this lead-in period must be used because it has been observed to decrease the incidence of rash).

The recommended oral dose of scored lamivudine, nevirapine and zidovudine twice daily in HIV-l-infected pediatric patients at least 3 months of age and weighing greater than or equal to 5 kg, after the lead-in period of nevirapine, is provided in Table 1. Lamivudine, Nevirapine and Zidovudine must be administered on an empty stomach, without food.

Prescribers should calculate the appropriate dose of Lamivudine, nevirapine and zidovudine for each child based on body weight (kg) and should not exceed the recommended adult dose. Half or whole tablets can be swallowed with water.

Table 1. Recommended Pediatric Dosage of Lamivudine, Nevirapine and Zidovudine Scored Tablets for Oral Suspension, 30 mg/50 mg/60 mg After the 14-Day Lead-In Period With Once-Daily Nevirapine

Weight Range (Body weight in kg)	Dosing	Lamivudine (AM dose in mg/ PM dose in mg)	Nevirapine (AM dose in mg/ PM dose in mg)	Zidovudine (AM dose in mg/ PM dose in mg)
5 to less than 7	1 tablet BID	30/30	50/50	60/60
7 to less than 11	1.5 tablets BID	45/45	75/75	90/90
11 to less than 14	2 tablets BID	60/60	100/100	120/120
14 to less than 18	2.5 tablets BID	75/75	125/125	150/150
18 to less than 22	3 tablets BID	90/90	150/150	180/180
22 to less than 25	3.5 tablets BID	105/105	175/175	210/210
25 and greater	Adult dose BID[a]			

a = For recommended doses of lamivudine 150 mg twice daily, nevirapine 200 mg twice daily and zidovudine 300 mg twice daily (adult maximum daily dose), the adult formulations (lamivudine 150 mg tablet, nevirapine 200 mg tablet and zidovudine 300 tablet) can be used.

Method of Preparation

For children unable to swallow the tablet(s), the following procedure can be used:

- Place the tablet(s) in container and add two teaspoonfuls (10 mL) of drinking water per tablet.
- Swirl the container until the tablet(s) breaks up into pieces small enough for the child to swallow. A spoon can be used to crush the pieces, if needed.
- Drink the mixture within 1 hour.
- Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX THE LAMIVUDINE, NEVIRAPINE AND ZIDOVUDINE TABLETS FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER. SPLIT TABLETS WHEN NEEDED. STORE UNUSED HALF TABLETS IN A SEPARATE BAG OR BOTTLE AND USE AS SOON AS PRACTICAL.

2.2 Monitoring Patients

Intensive clinical and laboratory monitoring, including liver enzyme tests, is essential at baseline and during the first 18 weeks of treatment with nevirapine-containing products. 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 enzyme tests at baseline, prior to dose escalation, and at two weeks post-dose escalation. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout nevirapine-containing products treatment [*see Warnings and Precautions (5)*]. In some cases, hepatic injury has progressed despite discontinuation of treatment.

2.3 Dose adjustment

Because Lamivudine, Nevirapine and Zidovudine is a fixed-dose combination formulation, it should not be prescribed for patients requiring dosage adjustment, such as those with reduced renal function (creatinine clearance less than 50 mL/min), patients on hemodialysis, patients with hepatic impairment, or patients experiencing dose-limiting adverse reactions.

Nevirapine

Patients with Rash

Discontinue nevirapine-containing products if a patient experiences severe rash or any rash accompanied by constitutional findings [*see Boxed Warning, Warnings and Precautions (5.2)*]. **Do not increase nevirapine dose if a patient experiences mild to moderate rash without constitutional symptoms during the 14-day lead-in period with once daily dosing until the rash has resolved** [*see Warnings and Precautions (5.2)*]. **The total duration of the once daily lead-in dosing period should not exceed 28 days at which point an alternative regimen should be sought.**

Patients with Hepatic Events

If a clinical (symptomatic) hepatic event occurs, permanently discontinue nevirapine. Do not restart nevirapine after recovery [*see Warnings and Precautions (5.1)*].

Patients with Dose Interruption

For patients who interrupt nevirapine dosing for more than 7 days, restart the recommended dosing, using one 200 mg tablet daily (150 mg/m^2/day in pediatric patients) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (150 mg/m^2 twice daily for pediatric patients).

3 DOSAGE FORMS AND STRENGTHS

Lamivudine, Nevirapine and Zidovudine tablets for oral suspension are scored, white to off-white circular biconvex tablets engraved LNZ on one side and break line on the other side.

4 CONTRAINDICATIONS

Lamivudine, Nevirapine and Zidovudine is contraindicated in patients with:

- Previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis, Stevens-Johnson syndrome) to any of the components of the product
- Moderate to Severe (Child-Pugh class B or C, respectively) hepatic impairment *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.7)]*
- For use as part of occupational and non- occupational post- exposure prophylaxis (PEP) regimens *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity and Hepatic Impairment

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-containing products. In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of subjects who received Nevirapine and 1% of subjects 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, subjects 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 subjects with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with Nevirapine use. Patients with signs or symptoms of hepatitis must be advised to discontinue Nevirapine-containing products and immediately seek medical evaluation, which should include liver enzyme tests.

Transaminases should be checked immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Transaminases should also be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if transaminases are initially normal or alternative diagnoses are possible [see Boxed Warning, Dosage and Administration (2.2)].

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, permanently discontinue Nevirapine-containing products. Do not restart Nevirapine-containing products after recovery. In some cases, hepatic injury progresses despite discontinuation of treatment.

The patients at greatest risk of hepatic events, including potentially fatal events, are women with high $CD4^+$ cell counts. In general, during the first 6 weeks of treatment, women have a 3-fold higher risk than men for symptomatic, often rash-associated, hepatic events (6% versus 2%), and patients with higher $CD4^+$ cell counts at initiation of Nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine-containing products. In a retrospective review, women with $CD4^+$ cell counts greater than 250 cells/mm^3 had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with $CD4^+$ cell counts less than 250 cells/mm^3 (11% versus 1%). An increased risk was observed in men with $CD4^+$ cell counts greater rthan 400 cells/mm^3 (6% versus 1% for men with $CD4^+$ cell counts less than 400 cells/mm^3). However, all patients, regardless of gender, $CD4^+$ cell count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all $CD4^+$ cell counts. Co-infection with hepatitis B or C and/or increased transaminase elevations at the start of therapy with nevirpaine-containing products are associated with a greater risk of later symptomatic events (6 weeks or more after starting Nevirapine therapy) and asymptomatic increases in AST or ALT.

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-1 uninfected individuals receiving multiple doses of nevirapine in the setting of post-exposure prophylaxis (PEP), an unapproved use. Use of Nevirapine for occupational and non-occupational PEP is contraindicated *[see Contraindications (4)]*.

Increased nevirapine trough concentrations have been observed in some patients with hepatic fibrosis or cirrhosis. Therefore, carefully monitor patients with either hepatic fibrosis or cirrhosis for evidence of drug-induced toxicity. Do not administer Nevirapine-containing products to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Contraindications (4), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

5.2 Skin Reactions

Severe and life-threatening skin reactions, including fatal cases, have been reported, occurring most frequently during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction including hepatic failure. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with Nevirapine use. In controlled clinical trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 2% of Nevirapine recipients compared to less than 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-containing products and seek medical evaluation immediately *[see Boxed Warning]*. Do not restart Nevirapine-containing products following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

If patients present with a suspected Nevirapine-associated rash, measure transaminases immediately. Permanently discontinue Nevirapine in patients with rash-associated transaminase elevations *[see Warnings and Precautions (5.1)]*.

Therapy with Nevirapine must be initiated with a 14-day lead-in period of once-daily dosing of 150 mg/m^2/day in pediatric patients (200 mg/day in adults), which has been shown to reduce the frequency of rash. Discontinue Nevirapine if a patient experiences severe rash or any rash accompanied by constitutional findings. Do not increase Nevirapine dose to a patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 150 mg/m^2/day in pediatric patients (200 mg/ day in adults) until the rash has resolved. The total duration of the once-daily lead-in dosing period must not exceed 28 days at which point an alternative regimen should be sought. Patients must be monitored closely if isolated rash of any severity occurs. Delay in stopping Nevirapine treatment after the onset of rash may result in a more serious reaction. Women appear to be at higher risk than men of developing rash with nevirapine.

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

5.3 Patients with HIV-1 and Hepatitis B Virus Co-infection

Post treatment Exacerbations of Hepatitis: In clinical trials in non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of hepatitis B viral DNA (HBV DNA). Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post marketing experience after changes from Lamivudine-containing HIV-1 treatment regimens to non-Lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of Lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follows 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.

Important Differences Among Lamivudine-Containing Products: **Lamivudine, Nevirapine and Zidovudine** contains a different dose of the same active ingredient (lamivudine) than EPIVIR-HBV® (lamivudine) Tablets and Oral Solution. EPIVIR-HBV was developed for treating chronic hepatitis B. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

Emergence of Lamivudine-Resistant HBV: In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response [see full prescribing information for EPIVIR-HBV (lamivudine) for additional information]. Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

5.4 Myopathy

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

5.5 Use with interferon- and ribavirin-based regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine, two components of Lamivudine, Nevirapine and Zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic

suppression) was seen when ribavirin was co administered with Lamivudine or Zidovudine in HIV-1/HCV co-infected patients *(see Clinical Pharmacology (12.3)]*, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and Lamivudine, Nevirapine and Zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of Lamivudine, Nevirapine and Zidovudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6) (see the complete prescribing information for interferon and ribavirin).
Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine-contaning products. Coadministration of ribavirin and zidovudine-contaning products is not advised.

5.6 Pancreatitis

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-containing products should be used with caution. Treatment with lamivudine-containing products should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur *[see Adverse Reactions (6.2)]*.

5.7 Immune Reconstitution Syndrome

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

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.8 Fat distribution

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

5.9 Use With Other, Lamivudine-, Zidovudine-, Nevirapine- and/or Emtricitabine-Containing Products

Lamivudine, Nevirapine and Zidovudine is a fixed-dose combination of lamivudine, nevirapine and zidovudine. Lamivudine, Nevirapine and Zidovudine should not be administered concomitantly with other lamivudine- or zidovudine-containing products including EPIVIR® (lamivudine), EPIVIR-HBV (lamivudine), RETROVIR® (zidovudine), COMBIVIR (lamivudine and zidovudine), EPZICOM® (abacavir sulfate and lamivudine), or TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine); or nevirapine-containing products, including Viramune (nevirapine) or Viramune XR (nevirapine); or emtricitabine-containing products, including ATRIPLA® (efavirenz, emtricitabine, and tenofovir), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine and tenofovir) or COMPLERA™ (rilpivirine, emtricitabine and tenofovir).

Nevirapine

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

5.10 Hematologic Toxicity/Bone Marrow Suppression

Zidovudine, a component of Lamivudine, Nevirapine and Zidovudine, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease. Lamivudine, Nevirapine and Zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count less than 1,000 cells/mm^3 or hemoglobin less than 9.5 g/dL *[see Adverse Reactions (6.1)]*.

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

5.11 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering lamivudine- and zidovudine-contaning products 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 zidovudine-contaning products 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).

5.12 Resistance

When discontinuing an antiretroviral regimen containing nevirapine, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than nevirapine are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop [*see Clinical Pharmacology (12.4)*].

5.13 Drug Interactions

See Table 8 for listings of established and potential drug interactions *[see Drug Interactions (7)]*.

Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products and Nevirapine is not recommended. Co-administration of St. John's wort with non-nucleoside reverse transcriptase inhibitors (NNRTIs), including Nevirapine, is expected to substantially decrease NNRTI concentrations and may result in sub-optimal levels of Nevirapine and lead to loss of virologic response and possible resistance to nevirapine or to the class of NNRTIs. Coadministration of nevirapine and efavirenz is not recommended as this combination has been associated with an increase in adverse reactions and no improvement in efficacy.

6. ADVERSE EVENTS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Life Threatening (including fatal) hepatotoxicity *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Skin reactions *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Symptomatic myopathy *[see Boxed Warning, Warnings and Precautions (5.4)]*.
- Acute exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.3)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C *[see Warnings and Precautions (5.5)]*.
- Exacerbation of anemia in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine *[see Warnings and Precautions (5.5)]*.
- Pancreatitis *[see Warnings and Precautions (5.6)]*.
- Hematologic toxicity, including neutropenia and anemia *[see Boxed Warning, Warnings and Precautions (5.10)]*.
- Lactic acidosis and hepatomegaly with steatosis *[see Boxed Warning, Warnings and Precautions (5.11)]*.

6.1 Clinical Trials in Adults

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

Lamivudine Plus Zidovudine Administered As Separate Formulations: In 4 randomized, controlled trials of lamivudine 300 mg per day plus zidovudine 600 mg per day, the following selected adverse reactions and laboratory abnormalities were observed (see Tables 2 and 3).

Table 2. Selected Clinical Adverse Reactions (≥5% Frequency) in Four Controlled Clinical Trials With Lamivudine 300 mg/day and Zidovudine 600 mg/day

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

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received lamivudine in controlled clinical trials *[see Warnings and Precautions (5.6)]*.

Selected laboratory abnormalities observed during therapy are listed in Table 3.

Table 3. Frequencies of Selected Laboratory Abnormalities Among Adults in Four Controlled Clinical Trials of Lamivudine 300 mg/day plus Zidovudine 600 mg/day[a]

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

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

n = Number of patients assessed.

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

Nevirapine

The most serious adverse reactions associated with nevirapine are hepatitis, hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction *[see Boxed Warning and Warnings and Precautions (5.1, 5.2)]*.

Hepatic Reaction

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of subjects who received Nevirapine and 1% of subjects in control groups. Female gender and higher CD4$^+$ cell counts in adults (greater than 250 cells/mm^3 in women and greater than 400 cells/mm^3 in men) place patients at increased risk of these events *[see Boxed Warning and Warnings and Precautions (5.1)]*.
Asymptomatic transaminase elevations (AST or ALT greater than 5X ULN) were observed in 6% (range 0% to 9%) of subjects who received Nevirapine and 6% of subjects in control groups. Co-infection with hepatitis B or C and/or increased transaminase elevations at the start of therapy with Nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting Nevirapine) and asymptomatic increases in AST or ALT.

Liver enzyme abnormalities (AST, ALT, GGT) were observed more frequently in subjects receiving nevirapine than in controls (see Table 5).

Skin Reaction
The most common clinical toxicity of nevirapine is rash, which can be severe or life-threatening *[see Boxed Warning and Warnings and Precautions (5.2)]*. Rash occurs most frequently within the first 6 weeks of therapy. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. In controlled clinical trials (Trials 1037, 1038, 1046, and 1090), Grade 1 and 2 rashes were reported in 13% of subjects receiving nevirapine compared to 6% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 2% of nevirapine recipients compared to less than 1% of subjects receiving placebo. Women tend to be at higher risk for development of Nevirapine-associated rash *[see Boxed Warning and Warnings and Precautions (5.2)]*.

Treatment-related, adverse experiences of moderate or severe intensity observed in greater than 2% of subjects receiving nevirapine in placebo-controlled trials are shown in Table 4.

Table 4: Percentage of Subjects with Moderate or Severe Drug-Related Events in Adult Placebo-Controlled Trials

	Trial 1090[1]		Trials 1037, 1038, 1046[2]	
	Nevirapine	**Placebo**	**Nevirapine**	**Placebo**
	(n=1121)	**(n=1128)**	**(n=253)**	**(n=203)**
Median exposure (weeks)	58	52	28	28
Any adverse event	15%	11%	32%	13%
Rash	5	2	7	2
Nausea	1	1	9	4
Granulocytopenia	2	3	<1	0
Headache	1	<1	4	1
Fatigue	<1	<1	5	4
Diarrhea	<1	1	2	1
Abdominal pain	<1	<1	2	0
Myalgia	<1	0	1	2

[1]Background therapy included lamivudine for all patients and combinations of NRTIs and PIs. Subjects had $CD4^+$ cell counts less than 200 cells/mm^3.

[2] Background therapy included zidovudine and zidovudine + didanosine; Nevirapine monotherapy was administered in some subjects. Subjects had $CD4^+$ cell count greater than or equal to 200 cells/mm^3.

Laboratory Abnormalities

Liver enzyme test abnormalities (AST, ALT) were observed more frequently in subjects receiving Nevirapine than in controls (Table 5). Asymptomatic elevations in GGT occur frequently but are not a contraindication to continue Nevirapine therapy in the absence of elevations in other liver enzyme tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing Nevirapine and control regimens (see Table 5).

Table 5: Percentage of Adult Subjects with Laboratory Abnormalities

	Trial 1090[1]		Trials 1037, 1038, 1046[2]	
	Nevirapine	**Placebo**	**Nevirapine**	**Placebo**
Laboratory Abnormality	**(n=1121)**	**(n=1128)**	**(n=253)**	**(n=203)**
Blood Chemistry				
SGPT (ALT) >250 U/L	5	4	14	4
SGOT (AST) >250 U/L	4	3	8	2
Bilirubin >2.5 mg/dL	2	2	2	2
Hematology				
Hemoglobin <8.0 g/dL	3	4	0	0
Platelets <50,000/mm^3	1	1	<1	2
Neutrophils <750/mm^3	13	14	4	1

[1]Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had $CD4^+$ cell counts less than 200 cells/mm^3.

[2] Background therapy included ZDV and ZDV+ddI; Nevirapine monotherapy was administered in some subjects. Subjects had $CD4^+$ cell count greater than or equal to 200 cells/mm^3.

6.2 Clinical trials in Pediatric Patients

Lamivudine

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these patients died of complications of pancreatitis. In a second open-label study (NUCA2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy *[see Warnings and Precautions (5.6)]*.

Paresthesias and Peripheral Neuropathies: Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study NUCA2002, 6 patients (9%) in Study NUCA2005, and 2 patients (<1%) in Study ACTG300.

Neonates - Clinical Trials in HIV-1: Limited short-term safety information is available from 2 small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at Week 38 or 36 of gestation *[see Clinical Pharmacology (12.3)]*. Selected adverse reactions reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, and sepsis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control groups limits assessments of causality, but it should be assumed that perinatally exposed infants may be at risk for adverse reactions comparable to those reported in pediatric and adult HIV-1-infected patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

Lamivudine and Zidovudine

Study ACTG 300: Selected clinical adverse reactions and physical findings with a ≥5% frequency during therapy with lamivudine Oral Suspension 4 mg/kg twice daily plus Zidovudine 160 mg/m^2 3 times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 6.

Table 6: Selected Clinical Adverse Reactions and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG 300

Adverse Reaction	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
Body as a whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%

Ear, Nose, and Throat		
Signs or symptoms of ears[a]	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

a = Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 7.

Table 7: Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients in Study ACTG 300

Test (Abnormal Level)	Lamivudine plus Zidovudine	Didanosine
Neutropenia (ANC<400 cells/mm3)	8%	3%
Anemia (Hgb<7.0 g/dL)	4%	2%
Thrombocytopenia (platelets<50,000/mm^3)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.

Zidovudine

Macrocytosis was reported in the majority of pediatric patients receiving Zidovudine180 mg/m^2 every 6 hours in open-label studies. Additionally, adverse reactions reported at an incidence of <6% in these studies were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, nervousness/irritability, and weight loss.

Nevirapine

Adverse events were assessed in BI Trial 1100.1032 (ACTG 245), a double-blind, placebo-controlled trial of Nevirapine (n=305) in which pediatric subjects received combination treatment with Nevirapine. In this trial two subjects were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Safety was also assessed in trial BI 1100.882 (ACTG 180), an open-label trial of nevirapine (n=37) in which subjects were followed for a mean duration of 33.9 months (range: 6.8 months to 5.3 years, including long-term follow-up in 29 of these subjects in trial BI 1100.892). The most frequently reported adverse events related to Nevirapine in pediatric subjects were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both Zidovudine and Nevirapine. Cases of allergic reaction, including one case of anaphylaxis, were also reported.

The safety of Nevirapine was also examined in BI Trial 1100.1368, an open-label, randomized clinical trial performed in South Africa in which 123 HIV-1 infected treatment-naïve subjects between 3 months and 16 years of age received combination treatment with Nevirapine oral suspension, Lamivudine and Zidovudine for 48 weeks *[see Use In Specific Populations (8.4) and Clinical Pharmacology (12.3)]*. Rash (all causality) was reported in 21% of the subjects, 4 (3%) of whom discontinued drug due to rash. All 4 subjects experienced the rash early in the course of therapy (less than 4 weeks) and resolved upon Nevirapine discontinuation. Other

clinically important adverse events (all causality) include neutropenia (9%), anemia (7%), and hepatotoxicity (2%) *[see Use In Specific Populations (8.4) and Clinical Studies (14.1)].*

Safety information on use of Nevirapine in combination therapy in pediatric subjects 2 weeks to less than 3 months of age was assessed in 36 subjects from the BI 1100.1222 (PACTG 356) trial. No unexpected safety findings were observed although granulocytopenia was reported more frequently in this age group compared to the older pediatric age groups and adults.

6.3 Post marketing experience

In addition to adverse reactions reported from clinical trials, the following reactions have been identified during post marketing use of lamivudine, nevirapine and zidovudine because they are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Lamivudine and Zidovudine:

Body as a whole: Redistribution/accumulation of body fat *[see Warnings and Precautions (5.8)].*
Cardiovascular: Cardiomyopathy
Endocrine and Metabolic: Hyperglycemia, gynecomastia.
Gastrointestinal: Oral mucosa pigmentation, stomatitis.
General: Weakness, vasculitis.
Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemia progressing on therapy), lymphadenopathy, splenomegaly.
Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, post treatment exacerbation of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.11, 5.3, 5.6)]*
Hypersensitivity: Sensitization reactions (including Anaphylaxis), urticaria.
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy, seizures.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

Nevirapine:

Body as a Whole: fever, somnolence, drug withdrawal *[see Drug Interactions (7)],* redistribution/accumulation of body fat *[see Warnings and Precautions (5.8)].*
Gastrointestinal: vomiting
Liver and biliary: jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure
Hematology: anemia, eosinophilia, neutropenia
Musculoskeletal: arthralgia, rhabdomyolysis associated with skin and/or liver reactions
Neurologic: paraesthesia
Skin and Appendages: allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue, or significant hepatic abnormalities *[see Warnings and Precautions (5.1)]* plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and/or renal dysfunction have been reported.

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

7. DRUG INTERACTIONS

No drug interactions studies have been conducted using Lamivudine and Zidovudine *[see Clinical Pharmacology (12.3)]*.

Lamivudine and Zidovudine

7.1 Antiretroviral Agents

Zidovudine: *Stavudine:* Concomitant use of Lamivudine, Nevirapine and Zidovudine with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated in vitro.
Nucleoside Analogues Affecting DNA Replication: Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of zidovudine against HIV-1; concomitant use of such drugs should be avoided.

7.2 Doxorubicin

Zidovudine: Concomitant use of Lamivudine, Nevirapine and Zidovudine with doxorubicin should be avoided since an antagonistic relationship with zidovudine has been demonstrated in vitro.

7.3 Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

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

7.4 Interferon- and Ribavirin-Based Regimens

Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.5), Clinical Pharmacology (12.3)]*.

7.5 Trimethoprim/Sulfamethoxazole (TMP/SMX)

Lamivudine: 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 PCP.

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

The specific pharmacokinetic changes that occur with co-administration of nevirapine and other drugs are listed in *Clinical Pharmacology*, Table 13**.** Clinical comments about possible dosage modifications based on established drug interactions are listed in Table 8. The data in Tables 8 and 9 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 also listed in Table 8. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for some classes of drugs listed in Table 8, additional clinical monitoring may be warranted when co-administering these drugs.

The *in vitro* interaction between nevirapine and the antithrombotic agent warfarin is complex. As a result, when giving these drugs concomitantly, plasma warfarin levels may change with the potential for increases in

coagulation time. When warfarin is co-administered with nevirapine, anticoagulation levels should be monitored frequently.

Table 8 Established and Potential Drug Interactions: Use With Caution, Alteration in Dose or Regimen May Be Needed Due to Drug Interaction Established Drug Interactions; See Clinical Pharmacology (12.3), Table 13 for Magnitude of Interaction

Drug Name	Effect on Concentration of Drug	Clinical Comment
Atazanavir/Ritonavir	↓ Atazanavir ↑ Nevirapine	Do not co-administer Nevirapine with atazanavir because Nevirapine substantially decreases atazanavir exposure.
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 Mycobacterium avium-intracellulare complex, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Efavirenz	↓ Efavirenz	There has been no determination of appropriate doses for the safe and effective use of this combination *[see Warnings and Precautions (5.13)]*.
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
Fosamprenavir	↓Amprenavir ↑Nevirapine	Co-administration of Nevirapine and fosamprenavir without ritonavir is not recommended.
Fosamprenavir/Ritonavir	↓Amprenavir ↑Nevirapine	No dosing adjustments are required when Nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir twice daily.
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 tablets to 500/125 mg twice-daily is recommended when used in

		combination with nevirapine. ~~A dose increase of lopinavir/ritonavir tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with Nevirapine in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence).~~ A dose increase of lopinavir/ritonavir oral solution to 533/133 mg twice daily with food is recommended in combination with Nevirapine. In children 6 months to 12 years of age receiving lopinavir/ritonavir solution, consideration should be given to increasing the dose of lopinavir/ritonavir to 13/3.25 mg/kg for those 7 to <15 kg; 11/2.75 mg/kg for those 15 to 45 kg; up to a maximum dose of 533/133 mg twice daily. Refer to the lopinavir/ritonavir package insert for complete pediatric dosing instructions when lopinavir/ritonavir tablets are used in combination with nevirapine.
Methadone	↓ Methadone	Methadone levels were decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone-maintained patients beginning Nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Nelfinavir	↓Nelfinavir M8 Metabolite ↓Nelfinavir C_{min}	The appropriate dose for nelfinavir in combination with Nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in Nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a Nevirapine-containing regimen may use rifabutin instead.
Saquinavir/ritonavir	The interaction between Nevirapine and saquinavir/ritonavir has not been evaluated	The appropriate doses of the combination of Nevirapine and saquinavir/ritonavir with respect to safety and efficacy have not been established.

Table 9: Potential Drug Interactions

Drug Class	Examples of Drugs	
Antiarrhythmic	Amiodarone, disopyramide, lidocaine	Plasma concentrations may be decreased.
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide	Plasma concentrations may be decreased
Antifungals	Itraconazole	Plasma concentrations of some azole antifungals may be decreased. Nevirapine and itraconazole should not be administered concomitantly due to a potential decrease in itraconazole plasma concentrations.
Calcium channel blockers	Diltiazem, nifedipine, verapamil	Plasma concentrations may be decreased.
Cancer chemotherapy	Cyclophosphamide	Plasma concentrations may be decreased.
Ergot alkaloids	Ergotamine	Plasma concentrations may be decreased.
Immuno suppressants	Cyclosporin, tacrolimus, sirolimus	Plasma concentrations may be decreased.
Motility agents	Cisapride	Plasma concentrations may be decreased.
Opiate agonists	Fentanyl	Plasma concentrations may be decreased.
Antithrombotic	Warfarin	Plasma concentrations may be increased. Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

8. USE IN SPECIFIC POPULAITONS

8.1 Pregnancy

Lamivudine and Zidovudine are Pregnancy Category C. Nevirapine is Pregnancy Category B. Therefore, Lamivudine, Nevirapine and Zidovudine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lamivudine and Zidovudine

Fetal Risk Summary: There are no adequate and well-controlled studies of lamivudine and zidovudine in pregnant women. Clinical trial data demonstrate that maternal zidovudine treatment during pregnancy reduces vertical transmission of HIV-1 infection to the fetus. Animal reproduction studies performed with lamivudine and zidovudine showed increased embryotoxicity and fetal malformations (zidovudine), and increased embryolethality (lamivudine).

Clinical Considerations: Treatment of HIV during pregnancy optimizes the health of both mother and fetus. Clinical trial data demonstrate that maternal zidovudine treatment significantly reduces vertical transmission of HIV-1 infection to the fetus. Published data suggest that combination antiretroviral regimens may reduce the rate of vertical transmission even further.

Pharmacokinetics of lamivudine and zidovudine in pregnant women are similar to the pharmacokinetics in nonpregnant women. No dose adjustments are needed during pregnancy.

In a clinical trial, adverse events among HIV-1-infected women were not different among untreated women and women treated with zidovudine. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients (see Human data below).

Data: ***Human Data:***

Lamivudine: Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies conducted in South Africa. The study assessed pharmacokinetics in: 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. Lamivudine pharmacokinetics in pregnant women were similar to those seen in nonpregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Zidovudine: A randomized, double-blind, placebo-controlled trial was conducted in HIV-1-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV-1 transmission.

Zidovudine treatment during pregnancy reduced the rate of maternal-fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to 7.8% for infants born to mothers treated with zidovudine. There were no differences in pregnancy-related adverse events between the treatment groups. Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. The observed abnormalities included problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug *[see Clinical Studies (14.1)]*.

Zidovudine pharmacokinetics were studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.

Animal Data:

Lamivudine: Animal reproduction studies performed at oral doses up to 130 and 60 times the adult dose in rats and rabbits, respectively, revealed no evidence of teratogenicity due to lamivudine. Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans. However, there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Based on animal studies, lamivudine crosses the placenta and is transferred to the fetus *[see Nonclinical Toxicology (13.2)]*.

Zidovudine**:** Increased fetal resorptions occurred in pregnant rats and rabbits treated with doses of zidovudine that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg dose of zidovudine. There were no other reported developmental anomalies. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily exposure [AUC] in humans given 600 mg/day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose *[see Nonclinical Toxicology (13.2)]*.

Nevirapine:

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

equivalent to or approximately 50% higher in rats and rabbits, respectively, than those seen at the recommended daily human dose (based on AUC). In rats, decreased fetal body weights were observed due to administration of a maternally toxic dose (exposures approximately 50% higher than that seen at the recommended human clinical dose).

There are no adequate and well-controlled trials of Nevirapine in pregnant women. The Antiretroviral Pregnancy Registry, which has been surveying pregnancy outcomes since January 1989, has not found an increased risk of birth defects following first trimester exposures to nevirapine. The prevalence of birth defects after any trimester exposure to nevirapine is comparable to the prevalence observed in the general population. Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirpaine therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with $CD4^+$ cell counts greater than 250 cells/mm^3 should not initiate nevirpaine unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women *[see Boxed Warning]*.

8.3 Nursing mothers

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

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

8.4 Pediatric Use

Lamivudine, Nevirapine and Zidovudine Tablets for Oral Suspension should not be administered to pediatric patients who are less than 3 months of age and weigh less than 5 kg because the safety and efficacy have not been established in this population.

8.6 Renal impairment

Patients with creatinine clearance less than 50 mL/min should not receive Lamivudine, Nevirapine and Zidovudine because it is a fixed-dose combination that cannot be adjusted.

8.7 Hepatic Impairment

Lamivudine, Nevirapine and Zidovudine is not recommended for patients with impaired hepatic function because it is a fixed-dose combination that cannot be adjusted.

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, do not administer nevirapine-containing products to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [*see Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)*].

10. OVERDOSAGE

Lamivudine, Nevirapine and Zidovudine: There is no known antidote for Lamivudine, Nevirapine and Zidovudine.

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Nevirapine: Cases of nevirapine overdose at doses ranging from 800 to 1800 mg per day for up to 15 days have been reported. Patients have experienced events including edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, and weight decrease. All events subsided following discontinuation of nevirapine.

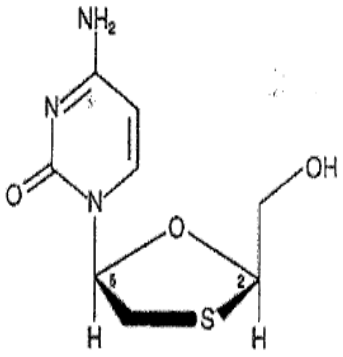
Zidovudine: Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, confusion, and 1 report of a grand mal seizure. Hematologic changes were transient. All patients recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, 3′-azido-3′-deoxy-5′-*O*- -*D*-glucopyranuronosylthymidine (GZDV), is enhanced.

11. DESCRIPTION

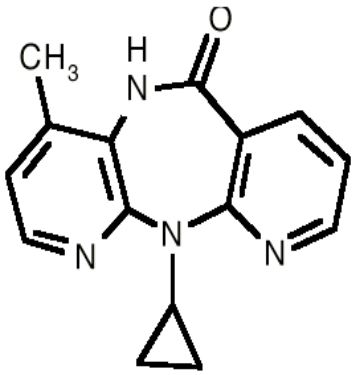
Lamivudine, Nevirapine and Zidovudine: Lamivudine, Nevirapine and Zidovudine Tablets for Oral Suspension are combination tablets containing lamivudine, nevirapine, and zidovudine. Lamivudine (3TC) and zidovudine (azidothymidine, AZT or ZDV) are synthetic nucleoside analogues with activity against HIV-1. Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against HIV-1.

Lamivudine, Nevirapine and Zidovudine tablets for oral suspension are for oral administration. Each tablet contains 30 mg of lamivudine, 50 mg of nevirapine, 60 mg of zidovudine and the inactive ingredients Colloidal Silicon Dioxide, Flavor Strawberry, Magnesium Stearate, Microcrystalline Cellulose, Lactose Monohydrate, Povidone (K-30), Purified Water, Sodium Starch Glycolate, and Sucralose.

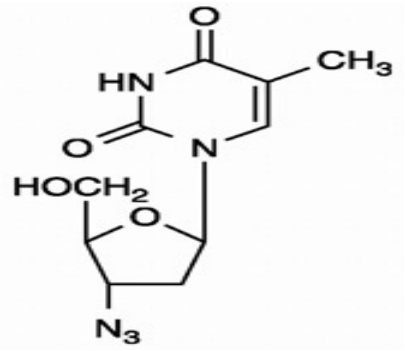
Lamivudine: The chemical name of Lamivudine is (2R,cis)-4- amino-1-(2-hydroxymethyl-1 ,3-oxathiolan-5-yl)-(1 H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has, also been referred to as (-)2' ,3'- dideoxy, 3'-thiacytidine. It has a molecular formula of $C_5H_{11}N_3O_3S$ and a molecular weight of 229.3. It has the following structural formula:



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



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



12. CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Lamivudine, Nevirapine and Zidovudine is an antiviral agent *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

Adults: Lamivudine, nevirapine and zidovudine combination tablets for oral suspension (30 mg/50 mg/60 mg) were bioequivalent to EPIVIR oral solution (containing lamivudine 10 mg/mL) of GlaxoSmithKline USA, RETROVIR oral solution (containing zidovudine 50 mg/5 mL) of GlaxoSmithKline USA, and Viramune tablets (containing 200 mg of nevirapine) of Boehringer Ingelheim Inc. USA, when single doses were administered to healthy volunteers under fasting conditions at a dose of lamivudine 120 mg, nevirapine 200 mg and zidovudine 240 mg (four combination tablets).

Effect of Food on Absorption of lamivudine, nevirapine and zidovudine: The effect of food on lamivudine, nevirapine and zidovudine was not determined; therefore, this product must be administered on an empty stomach, without food.

Lamivudine and Zidovudine

Lamivudine: The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 10. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

Zidovudine: The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 10. Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is GZDV. GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one-fifth of the zidovudine AUC.

Table 10. Pharmacokinetic Parameters[a] for Lamivudine and Zidovudine in Adults

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

[a] Data presented as mean ± standard deviation except where noted.

[b] Median [range].

[c] Children.

[d] Adults.

[e] Approximate range.

Nevirapine

Absorption and Bioavailability Nevirapine is readily absorbed (greater than 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 mcg/mL (7.5 micromolar) 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 mcg/mL (17 ± 7 micromolar), (n=242) were attained at 400 mg/day.

Distribution Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (Vdss) of nevirapine 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 Use in Specific Populations (8.3)*]. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 mcg/mL. Nevirapine concentrations in human

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

Metabolism/Elimination *In vivo* trials in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively bio transformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion trial in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of ^{14}C-nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (less than 5%) of the radioactivity in urine (representing less than 3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

Nevirapine is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A and 2B6. Nevirapine induces CYP3A and CYP2B6 by approximately 20-25%, as indicated by erythromycin breath test results and urine metabolites. Autoinduction of CYP3A and CYP2B6 mediated metabolism leads to an approximately 1.5- to 2fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma, from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

Specific Populations

Pregnancy: See Use in Specific Populations (8.1).

Lamivudine, nevirapine and zidovudine: No data are available.

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

Renal Impairment

Patients with creatinine clearance less than 50 mL/min should not receive Lamivudine, Nevirapine and Zidovudine because it is a fixed-dose combination that cannot be adjusted [*see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.6)*].

Hepatic Impairment

Nevirapine: In a steady-state study comparing 46 patients with mild (n=17; expansion of some portal areas; Ishak Score 1-2), moderate (n=20; expansion of most portal areas with occasional portal-to-portal and portal-to-central bridging; Ishak Score 3-4), or severe (n=9; marked bridging with occasional cirrhosis without decompensation indicating Child-Pugh A; Ishak Score 5-6) fibrosis as a measure of hepatic impairment, the multiple dose pharmacokinetic disposition of nevirapine and its five oxidative metabolites were not altered. However, approximately 15% of these patients with hepatic fibrosis had nevirapine trough concentrations above

9,000 µg/mL (2-fold the usual mean trough). Therefore, patients with hepatic impairment should be monitored carefully for evidence of drug-induced toxicity [*see Warnings and Precautions (5.10)*]. The patients studied were receiving antiretroviral therapy containing nevirapine 200 mg twice daily for at least 6 weeks prior to pharmacokinetic sampling, with a median duration of therapy of 3.4 years.

In a pharmacokinetic study where HIV-1 negative cirrhotic patients with mild (Child-Pugh A; n=6) or moderate (Child-Pugh B; n=4) hepatic impairment received a single 200 mg dose of nevirapine, a significant increase in the AUC of nevirapine was observed in one patient with Child-Pugh B and ascites suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, this single-dose study may not reflect the impact of hepatic impairment on multiple-dose pharmacokinetics.

Do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [*see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.7)*].

Gender

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

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

Pediatric Subjects

Lamivudine, nevirapine and zidovudine should not be administered to pediatric patients less than 3 months of age and weighing less than 5 kg.

Lamivudine: In Study NUCA2002, the pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-1-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and I.V. administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was 66% ± 26% (mean ± SD), which was less than the 86% ± 16% (mean ± SD) observed in adults. The mechanism for the diminished absolute bioavailabilty of lamivudine in infants and children is unknown.

Systemic clearance decreased with increasing age in pediatric patients, as shown in Figure 1.

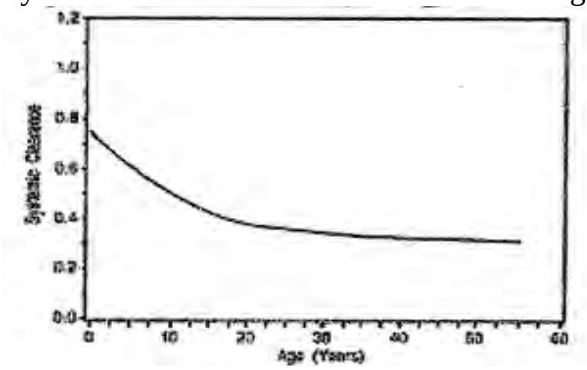


Figure 1: Systemic Clearance (L/hr.kg) of Lamivudine in Relation to Age

After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age, C_{max} was 1.1 ± 0.6 mcg/mL and the half-life was 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hour.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8 mg/kg/day dose and adults receiving a 4 mg/kg/day dose.

Distribution of lamivudine into the cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours post-dose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/mL.

Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants up to 1 week of age in 2 studies in South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients (>3 months of age) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age-ranges >3 months old *[see Adverse Reactions (6.?)]*.

Zidovudine: Zidovudine pharmacokinetics has been evaluated in HIV-infected pediatric patients (Table 11).

Patients 3 Months to 12 Years: Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90 to 240 mg/m^2 every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV. After intravenous dosing, about 29% of the dose was excreted in the urine unchanged, and about 45% of the dose was excreted as GZDV.

Table 11: Zidovudine Pharmacokinetic Parameters in Pediatric Patients[a]

Parameter	**Aged 3 Months to 12 Years**
Oral bioavailability (%)	65 ± 24 (n = 18)
CSF: Plasma ratio	0.68 [0.03 to 3.25][b] (n = 38)
CL (L/hr/kg)	1.85 ± 0.47 (n = 20)
Elimination half-life (hr)	1.5 ± 0.7 (n = 21)

a = Data presented as mean ± standard deviation except where noted
b = Median (range)

Nevirapine: Pharmacokinetic data for nevirapine have been derived from two sources: a 48-week pediatric trial in South Africa (BI Trial 1100.1368) involving 123 HIV-1 positive, antiretroviral-naïve patients aged 3 months to 16 years; and a consolidated analysis of five Pediatric AIDS Clinical Trials Group (PACTG) protocols comprising 495 patients aged 14 days to 19 years.

BI Trial 1100.1368 studied the safety, efficacy, and pharmacokinetics of a weight-based and a body surface area (BSA)-based dosing regimen of nevirapine. In the weight-based regimen, pediatric patients up to 8 years of age received a dose of 4 mg/kg once daily for two weeks followed by 7 mg/kg twice daily thereafter.

Patients 8 years and older were dosed 4 mg/kg once daily for two weeks followed by 4 mg/kg twice daily thereafter. In the BSA regimen, all pediatric patients received 150 mg/m^2 once daily for two weeks followed by 150 mg/m^2 twice daily thereafter [*see Use in Specific Populations (8.4) and Adverse Reactions (6.2)*]. Dosing of nevirapine at 150 mg/m^2 BID (after a two-week lead-in of 150 mg/m^2 QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 µg/mL (as targeted from adult data). In addition, the observed trough nevirapine concentrations were comparable between the two dosing regimens studied (BSA- and weight-based methods).

Drug Interactions: *See Drug Interactions (7)*

No drug interaction studies have been conducted using Lamivudine, Nevirapine, and Zidovudine. ~~However,~~ Table 12 and 13 present~~s~~ drug interaction information for ~~two of~~ the individual components of Lamivudine, Nevirapine, and Zidovudine.

Lamivudine Plus Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Table 12. Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC[a]

Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	**Lamivudine Dose**	**n**	**Lamivudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 150 mg	11	↑AUC 10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑AUC 43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	**Zidovudine Dose**	**n**	**Zidovudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78%[b]	↔
Clarithromycin 500 mg twice daily	100 mg q 4 hr x 7 days	4	↓AUC 12%	Range ↓34% to ↑14%	Not Reported
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64%[b]	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170%[b]	Not Assessed
Rifampin 600 mg daily x 14 days	200 mg q 8 hr X 14 days	8	↓AUC 47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130%[b]	Not Assessed

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

[a] This table is not all inclusive.

[b] Estimated range of percent difference.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of Lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and Lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected patients *[see Warnings and Precautions (5.5)]*.

Nevirapine: Nevirapine induces hepatic cytochrome P450 metabolic isoenzymes 3A and 2B6. Co-administration of Nevirapine and drugs primarily metabolized by CYP3A or CYP2B6 may result in decreased plasma concentrations of these drugs and attenuate their therapeutic effects.

While primarily an inducer of cytochrome P450 3A and 2B6 enzymes, nevirapine may also inhibit this system. Among human hepatic cytochrome P450s, nevirapine was capable *in vitro* of inhibiting the 10-hydroxylation of (R)-warfarin (CYP3A). The estimated Ki for the inhibition of CYP3A was 270 μM, a concentration that is unlikely to be achieved in patients as the therapeutic range is less than 25 μM. Therefore, nevirapine may have minimal inhibitory effect on other substrates of CYP3A.

Nevirapine does not appear to affect the plasma concentrations of drugs that are substrates of other CYP450 enzyme systems, such as 1A2, 2D6, 2A6, 2E1, 2C9, or 2C19. Table 13 contains the results of drug interaction trials performed with Nevirapine and other drugs likely to be co-administered. The effects of Nevirapine on the AUC, Cmax, and Cmin of co-administered drugs are summarized.

Table 13: Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Nevirapine (All interaction studies were conducted in HIV-1 positive patients)

Co-administered Drug	Dose of Co administered Drug	Dose Regimen of Nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
Antiretroviral				**AUC**	**C_{max}**	**C_{min}**
Atazanavir/Ritonavir[a, d]	300/100 mg QD day 4–13, then 400/100 mg QD, day 14–23	200 mg BID day 1-23. Subjects were treated with nevirapine prior to trial entry.	23	Atazanavir 300/100 mg ↓42 (↓52 to ↓29)	Atazanavir 300/100 mg ↓28 (↓40 to ↓14)	Atazanavir 300/100 mg ↓72 (↓80 to ↓60)
				Atazanavir 400/100 mg ↓19 (↓35 to ↑2)	Atazanavir 400/100 mg ↑2 (↓15 to↑24)	Atazanavir 400/100 mg ↓59 (↓73 to ↓40)
Darunavir/Ritonavir[e]	400/100 mg BID	200 mg BID	8	↑24 (↓3 to ↑57)	↑40 (↑14 to ↑73)	↑2 (↓21 to ↑32)
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)
Fosamprenavir	1400 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry.	17	↓33 (↓45 to ↓20)	↓25 (↓37 to ↓10)	↓35 (↓50 to ↓15)
Fosamprenavir/Ritonavir	700/100 mg BID	200 mg BID. Subjects were treated	17	↓11 (↓23 to ↑3)	⇔	↓19 (↓32 to ↓4)

		with nevirapine prior to trial entry				
Indinavir[a]	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir[a, b]	300/75 mg/m2 (lopinavir/ ritonavir)[b]	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15[c]	↓22 (↓44 to ↑9)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓19)
Lopinavir[a]	400/100 mg BID (lopinavir/ ritonavir)	200 mg QD x 14 days; 200 mg BID >1 year	22, 19[c]	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Maraviroc [f]	300 mg SD	200 mg BID	8	↑1 (↓35 to ↑55)	↑54 (↓6 to ↑151)	⇔
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	⇔	⇔	⇔
Stavudine	30-40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	⇔	⇔	§
Zalcitabine	0.125-0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	⇔	⇔	§
Zidovudine	100-200 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓28 (↓40 to ↓4)	↓30 (↓51 to ↑14)	§
Other Medications				**AUC**	**C_{max}**	**C_{min}**
Clarithromycin[a]	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓31 (↓38 to ↓24)	↓23 (↓31 to ↓14)	↓56 (↓70 to ↓36)
Metabolite 14-OH-clarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	⇔
Ethinyl estradiol[a] and	0.035 mg (as Ortho-Novum® 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	⇔	§
Norethindrone[a]	1 mg (as Ortho-			↓19 (↓30 to ↓7)	↓16 (↓27 to ↓3)	§

	Novum® 1/35)					
Depomedroxyprogesterone acetate	150 mg every 3 months	200 mg QD x 14 days; 200 mg BID x 14 days	32	⇔	⇔	⇔
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	⇔	⇔	⇔
Ketoconazole[a]	400 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	21	↓72 (↓80 to ↓60)	↓44 (↓58 to ↓27)	§
Methadone[a]	Individual Subject Dosing	200 mg QD x 14 days; 200 mg BID ≥7 days	9	In a controlled pharmacokinetic trial with 9 subjects receiving chronic methadone to whom steady-state nevirapine therapy was added, the clearance of methadone was increased by 3-fold, resulting in symptoms of withdrawal, requiring dose adjustments in 10 mg segments, in 7 of the 9 subjects. Methadone did not have any effect on nevirapine clearance.		
Rifabutin[a]	150 or 300 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↑17 (↓2 to ↑40)	↑28 (↑9 to ↑51)	⇔
Metabolite 25-O-desacetyl-rifabutin				↑24 (↓16 to ↑84)	↑29 (↓2 to ↑68)	↑22 (↓14 to ↑74)
Rifampin[a]	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑11 (↓4 to ↑28)	⇔	§

§ = C_{min} below detectable level of the assay
↑ = Increase, ↓ = Decrease, ⇔ = No Effect
[a] For information regarding clinical recommendations, see ***Drug Interactions (7)***.
[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.
[d] Parallel group design; n=23 for atazanavir/ritonavir + nevirapine, n=22 for atazanavir/ritonavir without nevirapine. Changes in atazanavir PK are relative to atazanavir/ritonavir 300/100 mg alone.
[e] Based on between-trial comparison.
[f] Based on historical controls.

Because of the design of the drug interaction trials (addition of 28 days of nevirapine therapy to existing HIV-1 therapy), the effect of the concomitant drug on plasma nevirapine steady-state concentrations was estimated by comparison to historical controls.

Administration of rifampin had a clinically significant effect on nevirapine pharmacokinetics, decreasing AUC and C_{max} by greater than 50%. Administration of fluconazole resulted in an approximate 100% increase in nevirapine exposure, based on a comparison to historic data [***see Drug Interactions (7)***]. The effect of other drugs listed in Table 12 on nevirapine pharmacokinetics was not significant. No significant interaction was observed when tipranavir was co-administered with low-dose ritonavir and nevirapine.

12.4 Microbiology

Mechanism of Action: ***Lamivudine:*** IntraceIlularly, 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-I reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3 TC- TP is a weak inhibitor of mammalian DNA polymerases α, ß, 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, ß, γ, or δ) are not inhibited by nevirapine.

Zidovudine: Intracellularly, zidovudine is phosphorylated to its active 5′-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

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

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

Nevirapine: The antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte-derived macrophages, and lymphoblastoid cell lines. In an assay using human embryonic kidney 293 cells, the median EC_{50} value (50% inhibitory concentration) of nevirapine was 90 nM against a panel of 2923 isolates of HIV-1 that were primarily (93%) clade B clinical isolates from the United States. The 99^{th} percentile EC_{50} value was 470 nM in this study. The median EC_{50} value was 63 nM (range 14-302 nM, n=29) against clinical isolates of HIV-1 clades A, B, C, D, F, G, and H, and circulating recombinant forms CRF01-AE, CRF02-AG and CRF12-BF. Nevirapine had no antiviral activity in cell culture against group of HIV-1 isolates (n=3) or HIV-2 isolates (n=3) replicating in cord blood mononuclear cells. Nevirapine in combination with Efavirenz exhibited strong antagonistic anti-HIV-1 activity in cell culture and was additive to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor enfuvirtide. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin in cell culture.

Zidovudine: The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The EC_{50} and EC90 values for zidovudine were 0.01 to 0.49 µM (1 µM = 0.27 mcg/mL) and 0.1 to 9 µM, respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC50 values of 0.011 µM (range: 0.005 to 0.110 µM) from Virco (n = 92 baseline samples from COL40263) and 0.0017 µM (0.006 to 0.0340 µM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC50 values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 µM, and against HIV-2 isolates from 0.00049 to

0.004 μM. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine,lamivudine, and zalcitabine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

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

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple amino acid substitutions, the most essential of which may be G333E. The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

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

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

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 1 and 2 trials over 1 to ≥12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine in cell culture. One or more of the RT mutations resulting in amino acid substitutions K103N, V106A, V108I, Y181C, Y188C, and G190A were detected in HIV-1 isolates from some patients as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the patients tested (n=24) had HIV-1 isolates with a >100-fold decrease in susceptibility to nevirapine in cell culture compared to baseline, and had one or more of the nevirapine-associated RT resistance substitutions. Nineteen of these patients (80%) had isolates with Y181C substitutions regardless of dose.

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

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

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

Lamivudine Plus Zidovudine: Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a substitution at codon 184, which confers resistance to lamivudine. Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below).

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

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

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13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Zidovudine: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279. In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 non metastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose. In rats, 2 late-appearing (after 20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species. At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

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

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

Zidovudine: Zidovudine was mutagenic in an L5178Y/TK+/- mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: *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 was lower than that measured in humans at the 200 mg twice daily dose. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included microbial assays for gene mutation (Ames: Salmonella strains and *E. coli*), mammalian cell gene mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is not known. In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of Nevirapine.

13.2 Reproductive and Developmental Toxicology Studies

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

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

Zidovudine: Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-

dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated AUC in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

14. CLINICAL STUDIES

14.1 Pediatric Patients

Lamivudine plus Zidovudine: ACTG 300 was a multi-center, randomized, double-blind study that provided for comparison of lamivudine plus zidovudine to didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naive pediatric patients were enrolled in these 2 treatment arms. The median age was 2.7 years (range: 6 weeks to 14 years), the mean baseline CD4+ cell count was 868 cells/mm^3, and the mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/mL. The median duration that patients remained on study was approximately 10 months. Results are summarized in Table 14.

Table 14 Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
HIV disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

Nevirapine: The pediatric safety and efficacy of Nevirapine was examined in BI Trial 1100.1368, an open-label, randomized clinical trial performed in South Africa in which 123 HIV-1 infected treatment-naïve subjects between 3 months and 16 years of age received Nevirapine oral suspension for 48 weeks. Subjects were divided into 4 age groups (3 months to less than 2 years, 2 to less than 7 years, 7 to less than 12 years, and 12 to less than or equal to 16 years) and randomized to receive one of two Nevirapine doses, determined by 2 different dosing methods [body surface area (150 mg/m^2) and weight-based dosing (4 or 7 mg/kg)] in combination with zidovudine and lamivudine [*see Adverse Reactions (6.2), Use in Specific Populations (8.4), and Clinical Pharmacology (12.3)*]. The total daily dose of Nevirapine did not exceed 400 mg in either regimen. There were 66 subjects in the body surface area (BSA) dosing group and 57 subjects in the weight-based (BW) dosing group.

Baseline demographics included: 49% male; 81% Black and 19% Caucasian; 4% had previous exposure to ARVs. Subjects had a median baseline HIV-1 RNA of 5.45 $\log_{10}$ copies/mL and a median baseline $CD4^+$ cell count of 527 cells/mm^3 (range 37-2279). One hundred and five (85%) completed the 48-week period while 18 (15%) discontinued prematurely. Of the patients who discontinued prematurely, 9 (7%) discontinued due to adverse reactions and 3 (2%) discontinued due to virologic failure. Overall the proportion of subjects who achieved and maintained an HIV-1 RNA less than 400 copies/mL at 48 weeks was 47% (58/123).

16. HOW SUPPLIED/ STORAGE AND HANDLING

Lamivudine, Nevirapine and Zidovudine Tablets for oral suspension, containing 30 mg lamivudine, 50 mg nevirapine and 60 mg zidovudine are scored, white to off-white circular biconvex tablets engraved LNZ on one side and break line on the other side. They are available as follows:

60 Tablets per bottle with desiccant sachets

Keep out of the reach and sight of children.

Do not store above 30^{o}C (86^{o}F). Store in the original package, protected from moisture. Keep the bottle tightly closed.

Do not use Lamivudine, Nevirapine and Zidovudine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

17. PATIENT COUNSELLING INFORMATION

See MEDICATION GUIDE

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

A Medication Guide is supplied as a tear-off following the full prescribing information.

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

Manufactured by:
Strides Arcolab Ltd
Bangalore 560001, India

November 2012

MEDICATION GUIDE

Lamivudine, Nevirapine and Zidovudine Tablets for Oral Suspension, 30 mg/50 mg/60 mg

Lamivudine (lah MIH vue deen), nevirapine (na VAIR a peen) and zidovudine,
(zye DOE vue deen)

Read this Medication Guide before your child starts taking Lamivudine, Nevirapine and Zidovudine and each time you get a refill. There may be new information. This information does not take the place of talking with your child's doctor.

What is the most important information one should know about taking Lamivudine, Nevirapine and Zidovudine?

Nevirapine (one component of Lamivudine, Nevirapine and Zidovudine) can cause serious side effects. These include severe liver and skin problems that can cause death. These problems can happen at any time during treatment, but the risk is highest during the first 18 weeks of treatment.

1. **Severe liver problems:** Anyone who takes nevirapine-containing products may get severe liver problems. In some cases these liver problems can lead to liver failure and the need for a liver transplant, or death.

People who have abnormal liver test results before starting nevirapine treatment and people with hepatitis B or C also have a greater chance of getting liver problems.

Your child may get a rash if he has liver problems.

Stop taking or giving nevirapine-containing procucts and call the doctor right away if your child has any of the following symptoms of liver problems:

- dark (tea colored) urine
- yellowing of your skin or whites of the eyes
- light-colored bowel movements (stools)
- fever
- nausea (feeling sick to the stomach)
- feel unwell or like you have the flu
- pain or tenderness on your right side below the ribs
- tiredness
- loss of appetite

Your child's doctor should see your child and do blood tests often to check the liver function during the first 18 weeks of treatment with nevirapine-containing products. You should continue to have your child's liver checked regularly during treatment with nevirapine. It is important to keep all of the doctor appointments.

2. **Severe rash and skin reactions:** Skin rash is the most common side effect of nevirapine. Most rashes happen in the first 6 weeks of taking nevirapine. **Rashes and skin reactions may be severe, life-threatening, and in some people, may lead to death. Stop using nevirapine-containing products and call the doctor right away if your child gets a rash with any of the following symptoms:**

- blisters
- mouth sores
- red or inflamed eyes, like "pink eye" (conjunctivitis)
- liver problems (see symptoms of liver problems above)
- swelling of the face
- fever
- feel unwell or like you have the flu
- tiredness
- muscle or joint aches

If your doctor tells you to stop treatment with nevirapine because your child has had any of the serious liver or skin problems described above, your child should never take nevirapine again.

See the section "What are the possible side effects of Lamivudine, Nevirapine and Zidovudine?" for more information.

What is Lamivudine, Nevirapine, and Zidovudine?

Lamivudine, Nevirapine and Zidovudine is a prescription medicine used to treat Human Immunodeficiency Virus (HIV), the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

Lamivudine, Nevirapine and Zidovudine contains 3 medicines; lamivudine nevirapine and zidovudine. Lamivudine and zidovudine are called nucleoside analogues reverse transcriptase inhibitors (NRTIs) and nevirapine is called non-nucleoside reverse transcriptase inhibitor (NNRTI). When used together, it helps lower the viral load and increase the number of CD4+ cells ("T cells"). CD4+ cells are a type of immune helper cell in the blood.

- Lamivudine, Nevirapine and Zidovudine does not cure HIV infection or AIDS
- It is not known if Lamivudine, Nevirapine and Zidovudine will help people live longer or have fewer of the medical problems that people get with HIV or AIDS
- It is very important to see a healthcare provider regularly while your child is taking Lamivudine, Nevirapine and Zidovudine

Who should not take Lamivudine, Nevirapine and Zidovudine?

Tell the doctor if your child has or has had liver problems. The doctor may tell you not to give nevirapine (one component of Lamivudine, Nevirapine and Zidovudine) if your child has certain liver problems.

Lamivudine, Nevirapine and Zidovudine is only for people diagnosed with HIV. If your child has not been diagnosed as HIV positive, then do not give Lamivudine, Nevirapine and Zidovudine.

What should I tell my child's doctor before giving Lamivudine, Nevirapine, and Zidovudine to my child?

Before you give nevirapine (a component of Lamivudine, Nevirapine, and Zidovudine), tell your doctor if your child:

- has or has had hepatitis (inflammation of the liver) or problems with the liver. See **"What is the most important information I should know about Lamivudine, Nevirapine, and Zidovudine?" and "Who should not take Lamivudine, Nevirapine, and Zidovudine?"**
- receives dialysis

- has skin problems, such as a rash
- has bone marrow suppression

Tell your child's doctor and pharmacist about all the medicines your child takes, including prescription and non-prescription medicines, vitamins and herbal supplements. Lamviduine, Nevirapine, and Zidovudine may affect the way other medicines work, and other medicines may affect how Lamviduine, Nevirapine, and Zidovudine works.

You should not give nevirapine-containing products if your child also takes:

- St. John's Wort. St. John's Wort can lower the amount of nevirapine in the body.
- efavirenz (Sustiva®, Atripla®). Efavirenz may cause your child to have an increased chance of side effects.
- atazanavir (Reyataz®)
- lopinavir and ritonavir (Kaletra®)
- fosamprenavir calcium (Lexiva®)
- itraconazole (Sporanox®)
- ketoconazole (Nizoral®)
- rifampin (Rifadin®, Rifamate®, Rifater®)

Also tell your doctor if your child takes:

- clarithromycin (Biaxin®)
- fluconazole (Diflucan®)
- indinavir sulfate (Crixivan®)
- methadone
- nelfinavir mesylate (Viracept®)
- rifabutin (Mycobutin®)
- warfarin (Coumadin®, Jantoven®)
- saquinavir mesylate (Invirase®)
- ganciclovir
- interferon alfa
- ribavirin

If you are not sure if your child takes a medicine above, ask your doctor or pharmacist.

Know the medicines you give to your child. Keep a list of them to show your child's doctor or pharmacist when your child gets a new medicine.

How should I give Lamivudine, Nevirapine, and Zidovudine to my child?

- Always give your child the exact amount of Lamivudine, Nevirapine and Zidovudine your child's doctor prescribes.
- Lamivudine, nevirapine, and zidovudine must be taken on an empty stomach, without food.
- Do not miss a dose of lamivudine, nevirapine, and zidovudine, because this could make the HIV harder to treat. If a dose is missed, give the missed dose right away. If it is almost time for the next

dose, do not give the missed dose, just give the next dose at the regular time. Do not give 2 doses at the same time.

- If your child stops taking lamivudine, nevirapine, and zidovudine for more than 7 days, ask your child's doctor how much to give before you start giving it again. You may need to start giving nevirapine once-a-day dosing again (different formulation of the drugs in this combination tablet), which is taken 1 time each day for 14 days.
- If you suspect that you have given too much lamivudine, nevirapine, and zidovudine, contact your local poison control center or emergency room right away.

The dose of Lamivudine, Nevirapine and Zidovudine for children is based on their size. Children's dosing of Lamivudine, Nevirapine, and Zidovudine starts after patients have taken 14 days of different formulations of lamivudine, nevirapine, and zidovudine. Check with your doctor to see what medication you should give your child during the first 14 days of nevirapine ("lead-in period") before starting Lamivudine, Nevirapine, and Zidovudine. Half or whole tablets can be swallowed with water. The usual dosing is as follows:

Table 1. Recommended ~~Pediatric~~ Dosage of Lamivudine, Nevirapine and Zidovudine Scored Tablets for Oral Suspension, 30 mg/50 mg/60 mg for Children After the 14-Day Lead-In Period With Once-Daily Nevirapine

Weight Range (Body weight in kg)	Dosing	Lamivudine (AM dose in mg/ PM dose in mg)	Nevirapine (AM dose in mg/ PM dose in mg)	Zidovudine (AM dose in mg/ PM dose in mg)
5 to less than 7	1 tablet BID	30/30	50/50	60/60
7 to less than 11	1.5 tablets BID	45/45	75/75	90/90
11 to less than 14	2 tablets BID	60/60	100/100	120/120
14 to less than 18	2.5 tablets BID	75/75	125/125	150/150
18 to less than 22	3 tablets BID	90/90	150/150	180/180
22 to less than 25	3.5 tablets BID	105/105	175/175	210/210
25 and greater	Adult dose BID[a]			

a = For recommended doses of lamivudine 150 mg twice daily, nevirapine 200 mg twice daily and zidovudine 300 mg twice daily (adult maximum daily dose), the adult formulations (lamivudine 150 mg tablet, nevirapine 200 mg tablet and zidovudine 300 tablet) can be used.

Method of Preparation

For children unable to swallow the tablet(s), the following procedure can be used:

- Place the tablet(s) in container and add two teaspoonfuls (10 mL) of drinking water per tablet.
- Swirl the container until the tablet(s) breaks up into pieces small enough for the child to swallow. A spoon can be used to crush the pieces, if needed.
- Drink the mixture within 1 hour.
- Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX THE LAMIVUDINE, NEVIRAPINE AND ZIDOVUDINE TABLETS FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER. SPLIT TABLETS WHEN NEEDED.

STORE UNUSED HALF TABLETS IN A SEPARATE BAG OR BOTTLE AND USE AS SOON AS PRACTICAL.

What are the possible side effects of Lamivudine, Nevirapine, and Zidovudine?

Lamivudine, Nevirapine and Zidovudine can cause:

- See **"What is the most important information I should know about Lamivudine, Nevirapine, and Zidovudine?"**
- **Changes in your child's immune system (Immune Reconstitution Syndrome)** can happen when your child starts taking HIV medicines. Your child's immune system may get stronger and begin to fight infections that have been hidden in the body for a long time. Tell your child's doctor if your child starts having new symptoms after starting the HIV medicine.
- **Changes in body fat** can happen in some people who take antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from your legs, arms, and face can also happen. The cause and long-term health effects of these problems are not known at this time.
- **Neutropenia and Anemia:** Serious blood problems including low levels of red and/or white blood cells have occurred with the use of zidovudine, one component of Lamivudine, Nevirapine and Zidovudine. Contact your child's doctor immediately if your child develops unusual fatigue, pale skin, sore throat, fever, or chills which may be signs of blood problems.
- **Lactic acidosis and liver problems**, including fatal cases, have been reported with the use of reverse transcriptase inhibitors, such as lamivudine and zidovudine, alone or in combination. Contact your child's doctor immediately if your child experiences 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.
- **Pancreatitis** is a dangerous inflammation of the pancreas. It may cause death. Tell your child's doctor right away if your child develops stomach pain, nausea, or vomiting. These can be signs of pancreatitis. Let your child's doctor know if your child has ever had pancreatitis, regularly drink alcoholic beverages, or have gallstones. Pancreatitis occurs more often in patients with these conditions. It is also more likely in people with advanced HIV disease, but can occur at any disease stage.
- **Worsening of hepatitis B virus (HBV) infection:** Patients with HBV infection, who take Lamivudine, Nevirapine, and Zidovudine and then stop it, may get "flare-ups" of their hepatitis. "Flare-up" is when the disease suddenly returns in a worse way than before. If your child has HBV infection, your doctor should closely monitor your child's liver function for several months after stopping Lamivudine, Nevirapine, and Zidovudine. You child may need to take anti-HBV medications.
- **Use with interferon- and ribavirin-based regimens:** Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C who are taking anti-HIV medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If your child is taking Lamivudine, Nevirapine, and Zidovudine as well as interferon with or without ribavirin and your child experiences side effects, be sure to tell your child's doctor.

Tell your child's doctor if your child has any side effect that bothers your child or that does not go away.

These are not all the possible side effects of Lamivudine, Nevirapine and Zidovudine. For more information, ask your child's doctor or pharmacist.

Call your child's doctor for medical advice about side effects. You may report side effects to Strides Inc. at (732)-839-1601 or FDA at 1-800-FDA-1088.

How do I store Lamivudine, Nevirapine, and Zidovudine?

Keep Lamivudine, Nevirapine and Zidovudine and all medicines out of the reach and sight of children.

Do not store above 30^{o}C (86^{o}F). Store in the original package, protected from moisture. Keep the bottle tightly closed.

Do not use Lamivudine, Nevirapine and Zidovudine after the expiry date which is stated on the label.

The expiry date refers to the last day of that month.

General information about Lamivudine, Nevirapine, and Zidovudine

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use Lamivudine, Nevirapine, and Zidovudine for a condition for which they were not prescribed. Do not give Lamivudine, Nevirapine, and Zidovudine to other people, even if they have the same condition your child has. They may harm them. This Medication Guide summarizes the most important information about Lamivudine, Nevirapine, and Zidovudine. If you would like more information, talk with your child's doctor. You can ask your child's pharmacist or doctor for information about these medications that is written for health professionals.

For any further information contact Strides Inc.

What are the ingredients in Lamivudine, Nevirapine, and Zidovudine?

Active ingredients: lamivudine, nevirapine and zidovudine

Inactive ingredients: Colloidal Silicon Dioxide, Flavor Strawberry, Magnesium Stearate, Microcrystalline Cellulose, Lactose Monohydrate, Povidone (K-30), Purified Water, Sodium Starch Glycolate, and Sucralose.

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