HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LAMIVUDINE, NEVIRAPINE, and ZIDOVUDINE tablets safely and effectively. See full prescribing information for LAMIVUDINE, NEVIRAPINE, and ZIDOVUDINE tablets.

LAMIVUDINE, NEVIRAPINE, and ZIDOVUDINE, tablets, for oral use
Initial U.S. Approval: XXXX

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXOCITY, SKIN REACTIONS, HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, EXACERBATIONS OF HEPATITIS B
See full prescribing information for complete boxed warning.

- **Fatal and non-fatal hepatotoxicity have been reported in patients taking nevirapine, a component of lamivudine, nevirapine, and zidovudine tablets. Discontinue immediately if clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur. Do not restart lamivudine, nevirapine, and zidovudine tablets after recovery. (5.1)**
- **Fatal and non-fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions, have been reported. Discontinue immediately if severe skin reactions, hypersensitivity reactions, or any rash with systemic symptoms occur. Check transaminase levels immediately for all patients who develop a rash in the first 18 weeks of treatment. Do not restart lamivudine, nevirapine, and zidovudine tablets after recovery. (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. (5.1, 5.2)**
- **Hematologic toxicity including neutropenia and severe anemia have been associated with the use of zidovudine, a component of lamivudine, nevirapine, and zidovudine tablets. (5.3)**
- **Symptomatic myopathy associated with prolonged use of zidovudine. (5.4)**
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including lamivudine and zidovudine, components of lamivudine, nevirapine, and zidovudine tablets. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.5)**
- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of lamivudine, nevirapine, and zidovudine tablets. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.6)**

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

Lamivudine, nevirapine, and zidovudine tablets, a combination of two nucleoside analogue reverse transcriptase inhibitors (lamivudine and zidovudine) and one non-nucleoside analogue reverse transcriptase inhibitor (nevirapine), is indicated alone as a complete regimen or in combination with other antiretroviral drugs for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg. (1)
Limitation of Use:
Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled trials, lamivudine, nevirapine, and zidovudine tablets is not recommended to be initiated, unless the benefit outweighs the risk, in:

- adult females with CD4+ cell counts greater than 250 cells per mm^3
- adult males with CD4+ cell counts greater than 400 cells per $mm^{3.}$ (1, 5.1)

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

- The 14-day lead-in period with nevirapine 200 mg once daily must be strictly followed; it has been demonstrated to reduce the frequency of rash. (2.3, 5.2)
- If any patient experiences rash during the 14-day lead-in period, do not dose escalate to 200 mg twice daily until the rash has resolved. Do not continue the lead-in dosing regimen beyond 28 days. (2.3)
- If dosing is interrupted for greater than 7 days, restart 14-day nevirapine lead-in period. (2.3)
- Because lamivudine, nevirapine, and zidovudine tablets is a fixed dose combination and cannot be dose adjusted, lamivudine, nevirapine, and zidovudine tablets is not recommended in pediatric patients weighing less than 35 kg, patients with creatinine clearance less than 50 mL per minute, patients with hepatic impairment or experiencing dose-limiting adverse reactions. (2.3, 8.4, 8.6, 8.7)

	Adults and Pediatric Patients Weighing at Least 35 kg
First 14 days	One lamivudine, nevirapine, and zidovudine fixed-dose tablet once daily followed by a daily oral dose of lamivudine and zidovudine 12 hours later
After 14 days	One lamivudine, nevirapine, and zidovudine fixed-dose tablet twice daily

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

Tablets: 150 mg lamivudine, 200 mg nevirapine, and 300 mg zidovudine. (3)

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

- In patients with previously hypersensitivity (4)
- In patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment (4, 5.1, 8.7)
- Use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens, an unapproved use (4, 5.1)

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

- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue lamivudine, nevirapine, and zidovudine tablets as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.7)
- Exacerbation of anemia has been reported in HIV 1/HCV co infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and zidovudine is not advised. (5.7)
- Pancreatitis: Use with caution in patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.8)
- Immune reconstitution syndrome and lipoatrophy have been reported in patients treated with combination antiretroviral therapy. (5.9, 5.12)

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

- Most commonly reported adverse reactions (incidence greater than or equal to 15%) in clinical trials of combination lamivudine and zidovudine were nausea, headache, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. (6.1)
- Nevirapine: The most common adverse reaction is rash. In adults the incidence of rash is 15% versus 6% with placebo, with Grade 3/4 rash occurring in 2% of subjects. (6.1)
- Nevirapine: In pediatric subjects the incidence of rash (all causality) was 21%. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Micro Labs USA, Inc. at 1-855-839-8195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

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

- Agents antagonistic with zidovudine: Concomitant use should be avoided. (7.1)
- Hematologic/bone marrow suppressive/cytotoxic agents: May increase the hematologic toxicity of zidovudine. (7.1)
- Sorbitol: Coadministration of lamivudine and sorbitol may decrease lamivudine concentrations; when possible, avoid chronic coadministration. (7.2)
- Co-administration of nevirapine 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. (5.10, 7.3, 12.3)

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

- Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)
- Monitor patients with hepatic fibrosis or cirrhosis carefully for evidence of drug induced toxicity. Do not administer lamivudine, nevirapine, and zidovudine tablets to patients with Child-Pugh B or C. (5.1, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXOCITY, SKIN REACTIONS, HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, and EXACERBATIONS OF HEPATITIS B

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FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXOCITY, SKIN REACTIONS, HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, and EXACERBATIONS OF HEPATITIS B

HEPATOTOXICITY: Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with nevirapine, a component of lamivudine, nevirapine, and zidovudine tablets. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher $CD4^+$ cell counts at initiation of therapy place patients at increased risk; women with $CD4^+$ cell counts greater than 250 cells per 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 for post-exposure prophylaxis (PEP). Use of nevirapine 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 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. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue lamivudine, nevirapine, and zidovudine tablets and seek medical evaluation immediately. Transaminase levels should be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. The 14-day lead-in period with nevirapine daily dosing has been observed to decrease the incidence of rash and must be followed [*see Warnings and Precautions (5.2)*].

MONITORING FOR HEPATOTOXICITY AND SKIN REACTIONS: Patients must be monitored intensively during the first 18 weeks of therapy with lamivudine, nevirapine, and zidovudine tablets 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 lamivudine, nevirapine, and zidovudine tablets following clinical hepatitis, or transaminase elevations combined with rash or other systemic symptoms, or following severe skin rash or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment.

HEMATOLOGIC TOXICITY: Zidovudine, a component of lamivudine, nevirapine, and zidovudine tablets, has 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 (5.3)]*.

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

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including lamivudine and zidovudine, two components of lamivudine, nevirapine, and zidovudine tablets. Discontinue lamivudine, nevirapine, and zidovudine tablets if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.5)]*.

EXACERBATIONS OF HEPATIS B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine, which is one component of lamivudine, nevirapine, and zidovudine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue lamivudine, nevirapine, and zidovudine and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.6)]*.

1 INDICATIONS AND USAGE

Lamivudine, nevirapine, and zidovudine tablets is indicated alone as a complete regimen or in combination with other antiretrovirals for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 35 kg.

Additional important use regarding the use of nevirapine, a component of lamivudine, nevirapine, and zidovudine tablets, for the treatment of HIV-1 infection:

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled trials, lamivudine, nevirapine, and zidovudine tablets is not recommended to be initiated, unless the benefit outweighs the risk in:
  - adult females with $CD4^+$ cell counts greater than 250 cells per mm^3 or
  - adult males with $CD4^+$ cell counts greater than 400 cells per mm^3 [*see Warnings and Precautions (5.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Adults and Pediatric Patients Weighing at Least 35 kg

Lead-in Period (First 14 days of dosing)

One lamivudine, nevirapine, and zidovudine fixed-dose tablet (containing 150 mg of lamivudine, 200 mg of nevirapine, and 300 mg of zidovudine) taken orally once daily followed by a daily oral dose of lamivudine 150 mg and zidovudine 300 mg 12 hours later.

Maintenance (After 14 days of dosing)
If the initial 14 days of dosing is tolerated without any incidence of rash, the recommended maintenance dose is one lamivudine, nevirapine, and zidovudine fixed-dose tablet (containing 150 mg of lamivudine, 200 mg of nevirapine, and 300 mg of zidovudine) taken orally twice daily.

Lamivudine, nevirapine, and zidovudine tablets can be taken with or without food.

2.2 Monitoring of Patients

Intensive clinical and laboratory monitoring, including liver enzyme tests, is essential at baseline and during the first 18 weeks of treatment with lamivudine, nevirapine, and zidovudine tablets. 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 18week period, frequent clinical and laboratory monitoring should continue throughout lamivudine, zidovudine, and nevirapine tablets treatment [*see Warnings and Precautions (5)*]. In some cases, hepatic injury has progressed despite discontinuation of treatment.

2.3 Dosage Adjustment

Because lamivudine, nevirapine, and zidovudine tablets is a fixed-dose combination and cannot be adjusted, it is not recommended for:

- pediatric patients weighing less than 35 kg *[see Use in Specific Populations (8.4)]*.
- patients with creatinine clearance less than 50 mL per minute *[see Use in Specific Populations (8.6)]*.
- patients with hepatic impairment *[see Use in Specific Populations (8.7)]*.
- patients experiencing dose-limiting adverse reactions.

Liquid and solid oral formulations of the individual components of lamivudine, nevirapine, and zidovudine tablets are available for these populations.

Patients with Rash
Discontinue lamivudine, nevirapine, and zidovudine tablets if a patient experiences severe rash or any rash accompanied by constitutional findings *[see 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 of 200 mg per day 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 lamivudine, nevirapine, and zidovudine tablets. Do not restart lamivudine, nevirapine, and zidovudine tablets after recovery *[see Warnings and Precautions (5.1)]*.

Patients with Dose Interruption
For patients who interrupt lamivudine, nevirapine, and zidovudine tablets dosing for more than 7 days, restart the recommended dosing of lamivudine, nevirapine, and zidovudine nevirapine tablets using the lead-in period dosing for 14 days.

3 DOSAGE FORMS AND STRENGTHS

Lamivudine, nevirapine, and zidovudine tablets contain 150 mg of lamivudine, 200 mg of nevirapine, and 300 mg of zidovudine. The tablets are white to off-white colored, capsule shaped, bevelled edged, biconvex, film-coated, debossed with “I” on one side and “47” on other side.

4 CONTRAINDICATIONS

Lamivudine, nevirapine, and zidovudine tablets are contraindicated:

- in patients with a previously hypersensitivity reaction to lamivudine, nevirapine, or zidovudine,
- in patients with moderate or 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, a component of lamivudine, nevirapine, and zidovudine. tablets. 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 nonspecific, 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. 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. Patients with signs or symptoms of hepatitis must be advised to discontinue lamivudine, nevirapine, and zidovudine tablets and immediately seek medical evaluation, which should include liver enzyme tests.

The first 18 weeks of therapy with nevirapine are a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life-threatening hepatic events. 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 treatment.

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 Dosage and Administration (2.2)]*.

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

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

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-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 lamivudine, nevirapine, and zidovudine tablets 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

Nevirapine, a component of lamivudine, nevirapine, and zidovudine tablets, has been associated with 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 lamivudine, nevirapine, and zidovudine tablets and seek medical evaluation immediately. Do not restart lamivudine, nevirapine, and zidovudine tablets following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

If patients present with a suspected nevirapine-associated rash, measure transaminases immediately. Permanently discontinue lamivudine, nevirapine, and zidovudine tablets 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 200 mg per day (150 mg per m^2 per day in pediatric patients), which has been shown to reduce the frequency of rash. Discontinue lamivudine, nevirapine, and zidovudine tablets if a patient experiences severe rash or any rash accompanied by constitutional findings. Do not increase lamivudine, nevirapine, and zidovudine tablets dose to a patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg per day (150 mg per m^2 per day in pediatric patients) 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 [*see*

Dosage and Administration (2.3)]. Patients must be monitored closely if isolated rash of any severity occurs. Delay in stopping lamivudine, nevirapine, and zidovudine tablets 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 per 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 Hematologic Toxicity/Bone Marrow Suppression

Zidovudine, a component of lamivudine, nevirapine, and zidovudine tablets, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease. Lamivudine, nevirapine, and zidovudine tablets should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count less than 1,000 cells per mm^3 or hemoglobin less than 9.5 grams per 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 tablets. Periodic blood counts are recommended for other HIV-1-infected patients. If anemia or neutropenia develops, dosage interruption may be needed.

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, a component of lamivudine, nevirapine, and zidovudine tablets, and therefore may occur with therapy with lamivudine, nevirapine, and zidovudine tablets.

5.5 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including lamivudine and zidovudine, components of lamivudine, nevirapine, and zidovudine tablets. A majority of these cases have been in women. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues. See full prescribing information for EPIVIR (lamivudine) and RETROVIR (zidovudine). Treatment with lamivudine, nevirapine, and zidovudine tablets 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).

5.6 Patients with Hepatitis B Virus Co-infection

<u>Posttreatment Exacerbations of Hepatitis:</u> Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine, a component of lamivudine,

nevirapine, and zidovudine tablets. See full prescribing information for EPIVIR (lamivudine). Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Emergence of Lamivudine-Resistant HBV: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV. Emergence of hepatitis B virus variants associated with resistance to lamivudine has been reported in HIV–1-infected subjects who have received lamivudine containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. See full prescribing information for EPIVIR (lamivudine).

5.7 Use with Interferon- and Ribavirin-Based Regimens

Patients receiving interferon alfa with or without ribavirin and lamivudine and zidovudine, components of lamivudine, nevirapine, and zidovudine tablets, should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. See full prescribing information for EPIVIR (lamivudine) and RETROVIR (zidovudine). Discontinuation of lamivudine, nevirapine, and zidovudine tablets 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 full prescribing information for interferon and ribavirin).

Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and lamivudine, nevirapine, and zidovudine tablets is not advised.

5.8 Pancreatitis

Lamivudine, nevirapine, and zidovudine tablets should be used with caution in patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis. Treatment with lamivudine, nevirapine, and zidovudine tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur *[see Adverse Reactions (6.1)]*.

5.9 Lipoatrophy

Treatment with zidovudine, a component of lamivudine, nevirapine, and zidovudine tablets, has been associated with loss of subcutaneous fat. The incidence and severity of lipoatrophy are related to cumulative exposure. This fat loss, which is most evident in the face, limbs, and buttocks, may be only partially reversible and improvement may take months to years after switching to a non-zidovudine-containing regimen. Patients should be regularly assessed for signs of lipoatrophy during therapy with zidovudine-containing products, and if feasible, therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy.

5.10 Drug Interactions

See Table 5 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, a component of lamivudine, nevirapine, and zidovudine tablets, 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.

5.11 Resistance

Nevirapine, a component of lamivudine, nevirapine, and zidovudine tablets, must not be used as a single agent to treat HIV-1 or added on as a sole agent to a failing regimen. Resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential for cross resistance. When discontinuing an antiretroviral regimen containing nevirapine, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than nevirapine are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop [*see Microbiology (12.4)*].

5.12 Immune Reconstitution Syndrome

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

6 ADVERSE REACTIONS

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

- Hematologic toxicity, including neutropenia and anemia *[see Boxed Warning, Warnings and Precautions (5.3)]*.
- Symptomatic myopathy *[see Boxed Warning, Warnings and Precautions (5.4)]*.
- Lactic acidosis and severe hepatomegaly with steatosis *[see Boxed Warning, Warnings and Precautions (5.5)]*.
- Exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.6)]*.

- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C *[see Warnings and Precautions (5.7)]*.
- Exacerbation of anemia in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine *[see Warnings and Precautions (5.7)]*.
- Pancreatitis *[see Warnings and Precautions (5.8)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (5.12)]*.
- Lipoatrophy *[see Warnings and Precautions (5.9)]*.

6.1 Clinical Trials Experience

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 and Zidovudine

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 1 and 2).

Table 1. Selected Clinical Adverse Reactions (Greater than or Equal to **5% Frequency) in 4 Controlled Clinical Trials with Lamivudine 300 mg per day and Zidovudine 600 mg per 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 (5.8)]*.

Selected laboratory abnormalities observed during therapy are listed in Table 2.

Table 2. Frequencies of Selected Laboratory Abnormalities Among Adults in 4 Controlled Clinical Trials of Lamivudine 300 mg per day plus Zidovudine 600 mg per day[a]

Test (Abnormal Level)	Lamivudine plus Zidovudine % (n)
Neutropenia (ANC<750/mm^3)	7.2% (237)
Anemia (Hgb<8 g/dL)	2.9% (241)
Thrombocytopenia (platelets<50,000/mm3)	0.4% (240)
ALT (>5 x ULN)	3.7% (241)
AST (>5 x ULN)	1.7% (241)
Bilirubin (>2.5 x ULN)	0.8% (241)
Amylase (>2 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

Clinical Trial Experience in Adult Patients: 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 (greater than 250 cells per mm^3 in women and

greater than 400 cells per 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 4).

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 3.

Table 3 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 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.

Laboratory Abnormalities

Liver enzyme test abnormalities (AST, ALT) were observed more frequently in subjects receiving nevirapine than in controls (Table 4). 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 4).

Table 4 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 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.

Clinical Trial Experience in Pediatric Patients

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. 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 Clinical Studies (14.2)]*.

6.2 Postmarketing Experience

Lamivudine and Zidovudine

The following reactions have been identified during post-approval use of lamivudine, nevirapine, and zidovudine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Redistribution/accumulation of body fat *[see Warnings and Precautions (5.9)]*.
Cardiovascular: Cardiomyopathy.
Endocrine and Metabolic: Gynecomastia, hyperglycemia.
Gastrointestinal: Oral mucosal pigmentation, stomatitis.
General: Vasculitis, weakness.
Hemic and Lymphatic: Anemia, (including pure red cell aplasia and anemias progressing on therapy), lymphadenopathy, splenomegaly.
Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.5), (5.6), (5.8)]*.
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 (5.9)*]
Gastrointestinal: vomiting
Liver and Biliary: jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure
Hematology: anemia, eosinophilia, neutropenia
Investigations: decreased serum phosphorus

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, drug reaction with eosinophilia and systemic symptoms (DRESS) [*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 postmarketing 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

7.1 Zidovudine

Agents Antagonistic with Zidovudine
Concomitant use of zidovudine with the following drugs should be avoided since an antagonistic relationship has been demonstrated in vitro:

- Stavudine
- Doxorubicine
- Nucleoside analogues, e.g., ribavirin

Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

Coadministration with the following drugs may increase the hematologic toxicity of zidovudine:

- Ganciclovir
- Interferon alfa
- Ribavirin
- Other bone marrow suppressive or cytotoxic agents

7.2 Lamivudine

Sorbitol
Coadministration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol-containing medicines with lamivudine-containing medicines *[see Clinical Pharmacology (12.3)]*.

7.3 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 7. Clinical comments about possible dosage modifications based on established drug interactions are listed in Table 5. The data in Tables 5 and 7 are based on the results of drug interaction trials 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 5. Although specific drug interaction trials in HIV-1 seropositive subjects have not been conducted for some classes of drugs listed in Table 5, additional clinical monitoring may be warranted when co-administering these drugs.

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

Table 5 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 6 for Magnitude of Interaction

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
HIV Antiviral Agents: Protease Inhibitors (PIs)		
Atazanavir/Ritonavir*	↓ Atazanavir ↑ Nevirapine	Do not co-administer nevirapine with atazanavir because nevirapine substantially decreases atazanavir exposure and there is a potential risk for nevirapine-associated toxicity due to increased nevirapine exposures.
Fosamprenavir* Fosamprenavir/Ritonavir*	↓Amprenavir ↑Nevirapine ↓Amprenavir ↑Nevirapine	Co-administration of nevirapine and fosamprenavir without ritonavir is not recommended. No dosing adjustments are required when nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir twice daily. The combination of nevirapine administered with fosamprenavir/ritonavir once daily has not been studied.
Indinavir*	↓ Indinavir	The appropriate doses of this combination of indinavir and nevirapine with respect to

		efficacy and safety have not been established.
Lopinavir/Ritonavir*	↓Lopinavir	Dosing in adult patients: A dose adjustment of lopinavir/ritonavir to 500/125 mg tablets twice daily or 533/133 mg (6.5 mL) oral solution twice daily is recommended when used in combination with nevirapine. Neither lopinavir/ritonavir tablets nor oral solution should be administered once daily in combination with nevirapine. Dosing in pediatric patients: Please refer to the Kaletra® prescribing information for dosing recommendations based on body surface area and body weight. Neither lopinavir/ritonavir tablets nor oral solution should be administered once daily in combination with nevirapine.
Nelfinavir*	↓Nelfinavir M8 Metabolite ↓Nelfinavir C_{min}	The appropriate doses of the combination of nevirapine and nelfinavir with respect to safety and efficacy have not been established.
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.
HIV Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz* Delavirdine Etravirine Rilpivirine	↓ Efavirenz	The appropriate doses of these combinations with respect to safety and efficacy have not been established. Plasma concentrations may be altered. Nevirapine should not be coadministered with another NNRTI as this combination has

		not been shown to be beneficial.
Hepatitis C Antiviral Agents		
Boceprevir	Plasma concentrations of boceprevir may be decreased due to induction of CYP3A4/5 by nevirapine.	Nevirapine and boceprevir should not be coadministered because decreases in boceprevir plasma concentrations may result in a reduction in efficacy.
Telaprevir	Plasma concentrations of telaprevir may be decreased due to induction of CYP3A4 by nevirapine and plasma concentrations of nevirapine may be increased due to inhibition of CYP3A4 by telaprevir.	Nevirapine and telaprevir should not be coadministered because changes in plasma concentrations of nevirapine, telaprevir, or both may result in a reduction in telaprevir efficacy or an increase in nevirapine-associated adverse events.
Other Agents		
Analgesics: 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.
Antiarrhythmics: Amiodarone, disopyramide, lidocaine	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Antibiotics: Clarithromycin* Rifabutin*	↓ Clarithromycin ↑ 14-OH clarithromycin ↑Rifabutin	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.

Rifampin*	↓ Nevirapine	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. 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.
Anticonvulsants: Carbamazepine, clonazepam, ethosuximide	Plasma concentrations of nevirapine and the anticonvulsant may be decreased.	Use with caution and monitor virologic response and levels of anticonvulsants.
Antifungals: Fluconazole* Ketoconazole* Itraconazole	↑Nevirapine ↓ Ketoconazole ↓ Itraconazole	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. Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug. Nevirapine and itraconazole should not be administered concomitantly due to potential decreases in itraconazole plasma concentrations that may reduce

		efficacy of the drug.
Antithrombotics: Warfarin	Plasma concentrations may be increased.	Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.
Calcium channel blockers: Diltiazem, nifedipine, verapamil	Plasma concentrations may be decreased.	Appropriate doses for these combinations have not been established.
Cancer chemotherapy: Cyclophosphamide	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Ergot alkaloids: Ergotamine	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus	Plasma concentrations may be decreased.	Appropriate doses for these combinations have not been established.
Motility agents: Cisapride	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Opiate agonists: Fentanyl	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.

Oral contraceptives: Ethinyl estradiol and Norethindrone*	↓ Ethinyl estradiol ↓ Norethindrone	Despite lower ethinyl estradiol and norethindrone exposures when coadministered with nevirapine, literature reports suggest that nevirapine has no effect on pregnancy rates among HIV-infected women on combined oral contraceptives. When coadministered with nevirapine, no dose adjustment of ethinyl estradiol or norethindrone is needed when used in combination for contraception. When these oral contraceptives are used for hormonal regulation during nevirapine therapy, the therapeutic effect of the hormonal therapy should be monitored.
***** The interaction between nevirapine and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.		

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Lamivudine and Zidovudine

Risk Summary

Available data from the Antiretroviral Pregnancy Registry (APR) show no difference in the overall risk of birth defects for lamivudine or zidovudine compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population *(see Data)*. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks' gestation. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral

administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the recommended clinical dose. Administration of oral zidovudine to female rats prior to mating and throughout gestation resulted in embryotoxicity at doses that produced systemic exposure (AUC) approximately 33 times higher than exposure at the recommended clinical dose. However, no embryotoxicity was observed after oral administration of zidovudine to pregnant rats during organogenesis at doses that produced systemic exposure (AUC) approximately 117 times higher than exposures at the recommended clinical dose. Administration of oral zidovudine to pregnant rabbits during organogenesis resulted in embryotoxicity at doses that produced systemic exposure (AUC) approximately 108 times higher than exposure at the recommended clinical dose. However, no embryotoxicity was observed at doses that produced systemic exposure (AUC) approximately 23 times higher than exposures at the recommended clinical dose *(see Data).*

Data

Human Data: Lamivudine: Based on prospective reports to the APR of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.8% (95% CI: 2.5% to 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trial 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. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)–fold greater compared with paired maternal serum concentration (n = 8).

Zidovudine: Based on prospective reports to the APR of over 13,000 exposures to zidovudine during pregnancy resulting in live births (including over 4,000 exposed in the first trimester), there was no difference between the overall risk of birth defects for zidovudine compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.2% (95% CI: 2.7% to 3.8%) following first trimester exposure to zidovudine-containing regimens and 2.8% (95% CI: 2.5% to 3.2%) following second/third trimester exposure to zidovudine-containing regimens.

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. Of the 363 neonates that were evaluated, 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 trial drug *[see Clinical Studies (14.2)]*.

Zidovudine has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery *[see Clinical Pharmacology (12.3)]*.

Animal Data: Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300, and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at system exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (C_{max}) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre-and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of lamivudine**.**

Zidovudine: A study in pregnant rats (at 50, 150, or 450 mg per kg per day starting 26 days prior to mating through gestation to postnatal Day 21) showed increased fetal resorptions at doses that produced systemic exposures (AUC) approximately 33 times higher than exposure at the recommended daily human dose (300 mg twice daily). However, in an oral embryo-fetal development study in rats (at 125, 250, or 500 mg per kg per day on gestation Days 6 through 15), no fetal resorptions were observed at doses that produced systemic exposure (AUC) approximately 117 times higher than exposures at the recommended daily human dose. An oral embryo-fetal development study in rabbits (at 75, 150, or 500 mg per kg per day on gestation Days 6 through 18) showed increased fetal resorptions at the 500 mg-per-kg-per-day dose, which produced systemic exposures (AUC) approximately 108 times higher than exposure at the recommended daily human dose; however, no fetal resorptions were noted at doses up to 150 mg per kg per day, which produced systemic exposure (AUC) approximately 23 times higher than exposures at the recommended daily human dose. These oral embryo-fetal development studies in the rat and rabbit revealed no evidence of fetal malformations with zidovudine. In another developmental toxicity study, pregnant rats (dosed at 3,000 mg per kg per day from Days 6 through 15 of gestation) showed marked maternal toxicity and an increased incidence of fetal malformations at exposures greater than 300 times the recommended daily human dose based on AUC. However, there were no signs of fetal malformations at doses up to 600 mg per kg per day.

Nevirapine

Risk Summary

Available data from the APR show no difference in the risk of overall major birth defects for nevirapine compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the MACDP *[see Data]*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

In literature reports, immediate-release nevirapine exposure (C_{min}) can be up to 29% lower during pregnancy. However, as this reduction was not found to be clinically meaningful, dose adjustment is not necessary *[see Data]*.

There is a risk for severe hepatic events in pregnant women exposed to nevirapine *[see Clinical Considerations]*. In animal reproduction studies, no evidence of adverse developmental outcomes were observed following oral administration of nevirapine during organogenesis in the rat and rabbit, at systemic exposures (AUC) to nevirapine approximately equal (rats) and 50% higher (rabbits) than the exposure in humans at the recommended 400 mg daily dose *[see Data]*.

Clinical Considerations

Maternal adverse reactions
Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with $CD4^+$ cell counts greater than 250 cells/mm^3 should not initiate nevirapine unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women *[see Warnings and Precautions (5.1)]*.

Data
Human Data
Based on prospective reports to the APR of over 2600 exposures to nevirapine during pregnancy resulting in live births (including over 1100 exposed in the first trimester), there was no difference between nevirapine and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.8% (95% CI: 1.9 %, 4.0%) following first trimester exposure to nevirapine- containing regimens and 3.2% (95% CI: 2.4%, 4.3%) for second/third trimester exposure to nevirapine-containing regimens.

There are several literature reports of chronic administration of immediate-release nevirapine during pregnancy, in which nevirapine pharmacokinetics were compared between pregnancy and

postpartum. In these studies, the mean difference in nevirapine C_{min} during pregnancy as compared to postpartum ranged from no difference to approximately 29% lower.

Animal Data
Nevirapine was administered orally to pregnant rats (at 0, 12.5, 25, and 50 mg per kg per day), and rabbits (at 0, 30, 100, and 300 mg per kg per day through organogenesis (on gestation days 7 through 16, and 6 through 18, respectively). No adverse developmental effects were observed at doses producing systemic exposures (AUC) approximately equivalent to (rats) or approximately 50% higher (rabbits) than human exposure at the recommended daily dose. In rats, decreased fetal body weights were observed at a maternally toxic dose at an exposure approximately 50% higher than the recommended daily dose.

8.2 Lactation

Lamivudine, Nevirapine, and Zidovudine

Risk Summary

The Centers for Disease Control and Prevention recommends that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Lamivudine and zidovudine are present in human milk. Published data report that nevirapine is present in human milk *[see Data]*. There are limited data on the effects of nevirapine on the breastfed infant. There is no information on the effects of lamivudine or zidovudine on the breastfed infant or the effects of lamivudine, nevirapine, or zidovudine on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving lamivudine, nevirapine, and zidovudine tablets.

Nevirapine

Data

Based on five publications, immediate-release nevirapine was excreted in breast-milk at median concentrations ranging from 4080 to 6795 ng per mL, and the median maternal breast-milk to maternal plasma concentration ratio range was 59 to 88%. Reported infant nevirapine median plasma concentrations were low, ranging from 734 to 1140 ng per mL. The estimated nevirapine dose of 704 to 682 µg per kg per day for infants fed exclusively with breast-milk was lower than the daily recommended nevirapine dose for infants. Published literature indicates that rash and hyperbilirubinemia have been seen in infants exposed to nevirapine through breastmilk.

8.4 Pediatric Use

Lamivudine, nevirapine, and zidovudine tablets is not recommended for use in pediatric patients who weigh less than 35 kg because it is a fixed-dose combination that cannot be adjusted for these patient population *[see Dosage and Administration (2.1)]*.

8.5 Geriatric Use

Clinical studies of lamivudine, nevirapine, and zidovudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of lamivudine, nevirapine, and zidovudine tablets in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Reduction of the dosage of lamivudine and zidovudine is recommended for patients with impaired renal function. Patients with creatinine clearance less than 50 mL per min should not receive lamivudine, nevirapine, and zidovudine tablets because it is a fixed-dose combination that cannot be adjusted.

8.7 Hepatic Impairment

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Lamivudine, nevirapine, and zidovudine tablets 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 lamivudine, nevirapine, and zidovudine tablets 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

There is no known specific treatment for overdose with lamivudine, zidovudine, or nevirapine. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

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

Zidovudine: Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. No specific symptoms or signs have been identified following acute overdosage with zidovudine apart from those listed as adverse events such as fatigue, headache, vomiting, and occasional reports of hematological disturbances. Patients recovered without permanent sequelae. 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-β-D-glucopyranuronosylthymidine (GZDV), is enhanced.

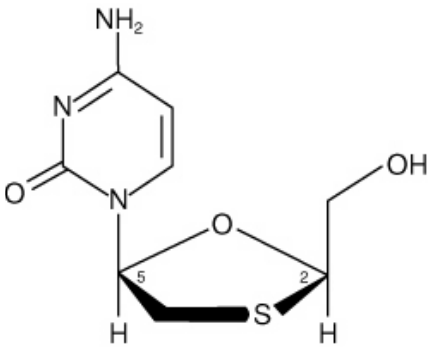
Nevirapine: Cases of nevirapine overdose at doses ranging from 800 to 1800 mg per day for up to 15 days have been reported. Patients have experienced events including edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, and weight decrease.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

11 DESCRIPTION

Lamivudine, nevirapine, and zidovudine tablets contain two synthetic nucleoside analogue (lamivudine and zidovudine also known as azidothymidine, or ZDV) and non-nucleoside reverse transcriptase inhibitor (nevirapine) with inhibitory activity against HIV-1.

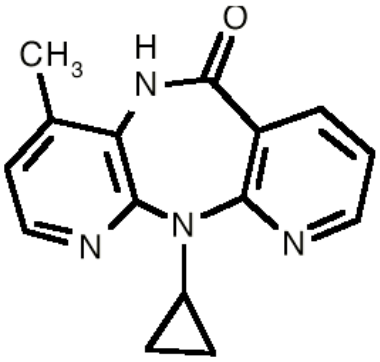
Lamivudine, nevirapine, and zidovudine tablets are for oral administration. Each film-coated tablet contains the active ingredients 150 mg of lamivudine USP, 200 mg of nevirapine USP, and 300 mg of zidovudine USP and the inactive ingredients are colloidal silicon dioxide, hydroxy propyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone k-25, and sodium starch glycolate. The tablets are coated with opadry white 13b58894, that is made of hypromellose, polyethylene glycol 400, polysorbate 80 and titanium dioxide.

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



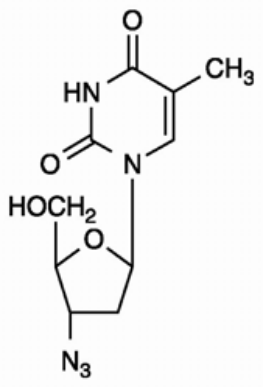
Lamivudine USP is a white to off-white crystalline powder with a solubility of approximately 70 mg/mL in water at 20°C.

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



Nevirapine USP is a white to off-white odorless to nearly odorless crystalline powder.

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lamivudine, nevirapine, and zidovudine are antiviral agents *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

Lamivudine and Zidovudine
Lamivudine: 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: 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.
The pharmacokinetic properties of lamivudine and zidovudine in fasting subjects are summarized in Table 6.

Table 6. 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/h/kg)	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/h/kg)	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (h)[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 per 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 per day. Steady-state trough nevirapine concentrations of 4.5 ± 1.9 mcg per mL (17 ± 7 micromolar), (n=242) were attained at 400 mg per day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high-fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox® 30 mL), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate trial in HIV-1 infected subjects (n=6), nevirapine steady-state systemic exposure (AUC_{τ}) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without food, antacid or didanosine.

Distribution

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 per 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 (8.2)]*. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 mcg per 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 biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion 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 2-fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg per 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 per day.

Effect of Food on Absorption of Lamivudine, Nevirapine, and Zidovudine: Lamivudine, nevirapine, and zidovudine tablets may be administered with or without food.

Special Populations: *Renal Impairment: Lamivudine and Zidovudine:* The effect of renal impairment on the combination of lamivudine and zidovudine has not been evaluated (see the U.S. prescribing information for the individual lamivudine and zidovudine components).

Nevirapine: HIV-1 seronegative adults with mild (CrCL 50-79 mL per min; n=7), moderate (CrCL 30-49 mL per min; n=6), or severe (CrCL less than 30 mL per min; n=4) renal impairment received a single 200 mg dose of nevirapine in a pharmacokinetic trial. These

subjects did not require dialysis. The trial included six additional subjects with renal failure requiring dialysis.

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. However, subjects requiring dialysis exhibited a 44% reduction in nevirapine AUC over a one-week exposure period. There was also evidence of accumulation of nevirapine hydroxy-metabolites in plasma in subjects requiring dialysis. An additional 200 mg dose following each dialysis treatment is indicated.

Hepatic Impairment: *Lamivudine, Nevirapine, and Zidovudine Tablets:* Do not administered lamivudine, nevirapine, and zidovudine tablets 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)]*.

Lamivudine and Zidovudine: The effect of hepatic impairment on the combination of lamivudine and zidovudine has not been evaluated (see the U.S. prescribing information for the individual lamivudine and zidovudine components).

Nevirapine: In a steady-state trial comparing 46 subjects 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 subjects with hepatic fibrosis had nevirapine trough concentrations above 9,000 mcg per 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 (5.1)]*. The subjects 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 trial where HIV-1 negative cirrhotic subjects 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 subject 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 trial may not reflect the impact of hepatic impairment on multiple-dose pharmacokinetics.

Pregnant Women: *Lamivudine*: Lamivudine pharmacokinetics were studied in 36 pregnant women during 2 clinical trials conducted in South Africa. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Zidovudine: Zidovudine pharmacokinetics have been studied in a Phase 1 trial of 8 women during the last trimester of pregnancy. Zidovudine pharmacokinetics were similar to those of non-pregnant 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.

Pediatric Patients: Lamivudine, nevirapine, and zidovudine tablets should not be administered to pediatric patients weighing less than 35 kg.

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

Male and Female Patients:
Lamivudine and zidovudine: There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components (lamivudine or zidovudine) based on the available information that was analyzed for each of the individual components.

Nevirapine: In the multinational 2NN trial, a population pharmacokinetic substudy of 1077 subjects was performed that included 391 females. Female subjects 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.

Racial Groups:
Lamivudine: There are no significant or clinically relevant racial differences in lamivudine pharmacokinetics based on the available information that was analyzed for the individual lamivudine component.
Zidovudine: The pharmacokinetics of zidovudine with respect to race have not been determined.

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

Black subjects (n=80/group) in Trial 1100.1486 showed approximately 30% to 35% higher trough concentrations than Caucasian subjects (250-325 subjects/group) in both immediate-release nevirapine and nevirapine extended-release tablets treatment groups over 96 weeks of treatment at 400 mg per day.

Drug Interactions *[see Drug Interactions (7)]*

No drug interaction trials have been conducted using lamivudine, nevirapine, and zidovudine tablets.

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

Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects.

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 subjects.

Sorbitol (Excipient): Lamivudine and sorbitol solutions were coadministered to 16 healthy adult subjects in an open-label, randomized-sequence, 4-period, crossover trial. Each subject received a single 300-mg dose of lamivudine oral solution alone or coadministered with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol in solution. Coadministration of lamivudine with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the $AUC_{(0-24)}$; 14%, 32%, and 36% in the $AUC_{(\infty)}$; and 28%, 52%, and 55% in the C_{max}: of lamivudine, respectively.

Table 6 presents drug interaction information for the individual components of lamivudine and zidovudine.

Table 6. Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC[a]

Coadministered Drug and Dose	Drug and Dose	n	Concentrations of Lamivudine or Zidovudine		Concentration of Coadministered Drug
			AUC	Variability	
Nelfinavir 750 mg every 8 h x 7 to 10 days	Lamivudine single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	Lamivudine single 300 mg	14	↑43%	90% CI: 32% to 55%	↔
Atovaquone 750 mg every 12 h with food	Zidovudine 200 mg every 8 h	14	↑31%	Range: 23% to 78%[b]	↔
Clarithromycin 500 mg twice daily	Zidovudine 100 mg every 4 h x 7 days	4	↓12%	Range: ↓34% to ↑14%	Not Reported
Fluconazole 400 mg daily	Zidovudine 200 mg every	12	↑74%	95% CI: 54% to 98%	Not Reported

	8 h				
Methadone 30 to 90 mg daily	Zidovudine 200 mg every 4 h	9	↑43%	Range: 16% to 64%[b]	↔
Nelfinavir 750 mg every 8 h x 7 to 10 days	Zidovudine single 200 mg	11	↓35%	Range: 28% to 41%	↔
Probenecid 500 mg every 6 h x 2 days	Zidovudine 2 mg/kg every 8 h x 3 days	3	↑106%	Range: 100% to 170%[b]	Not Assessed
Rifampin 600 mg daily x 14 days	Zidovudine 200 mg every 8 h x 14 days	8	↓47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg every 6 h x 4 days	Zidovudine 200 mg every 8 h x 4 days	9	↓25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg every 8 h x 4 days	Zidovudine 100 mg every 8 h x 4 days	6	↑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.

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 K_i for the inhibition of CYP3A was 270 micromolar, a concentration that is unlikely to be achieved in patients as the therapeutic range is less than 25 micromolar. 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 7 (see below) 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, C_{max}, and C_{min} of co-administered drugs are summarized.

Table 7 Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Nevirapine (All interaction studies were conducted in HIV-1 positive subjects)

Co-administered	Dose of Co-	Dose	n	% Change of Co-administered Drug

Drug	administered Drug	Regimen of Nevirapine		Pharmacokinetic Parameters (90% CI)		
Antiretrovirals				**AUC**	**C_{max}**	**C_{min}**
Atazanavir/Ritonavir[a, d]	300/100 mg QD day 4 to 13, then 400/100 mg QD, day 14 to 23	200 mg BID day 1 to 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 to 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 with nevirapine prior to trial entry	17	↓11 (↓23 to ↑3)	⇔	↓19 (↓32 to ↓4)
Indinavir[a]	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir[a, b]	300/75 mg/m^2 (lopinavir/	7 mg/kg or 4 mg/kg QD x 2 weeks;	12, 15[c]	↓22 (↓44 to ↑9)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓19)

	ritonavir) [b]	BID x 1 week				
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 to 40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	⇔	⇔	§
Zalcitabine	0.125 to 0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	⇔	⇔	§
Zidovudine	100 to 200 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓28 (↓40 to ↓4)	↓30 (↓51 to ↑14)	§
Other Medications				**AUC**	**C_{max}**	**C_{min}**
Clarithromycin[a]	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓31 (↓38 to ↓24)	↓23 (↓31 to ↓14)	↓56 (↓70 to ↓36)
Metabolite 14-OH-clarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	⇔
Ethinyl estradiol[a] and Norethindrone[a]	0.035 mg (as Ortho-Novum® 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	⇔	§
	1 mg (as Ortho-Novum® 1/35)			↓19 (↓30 to ↓7)	↓16 (↓27 to ↓3)	§

Depomedroxy-progesterone 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 Patient 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 7 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: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

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

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.

Antiviral Activity:

Lamivudine plus Zidovudine: In HIV–1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios was not antagonistic.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and fresh human peripheral blood lymphocytes (PBMCs) using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Zidovudine: The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines including monocytes and fresh human peripheral blood lymphocytes. The EC_{50} and EC_{90} values for zidovudine were 0.01 to 0.49 microM (1 microM = 0.27 mcg per mL) and 0.1 to

9 microM, respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.011 microM (range: 0.005 to 0.110 microM) from Virco (n = 92 baseline samples) and 0.0017 microM (range: 0.006 to 0.0340 microM) from Monogram Biosciences (n = 135 baseline samples). The EC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 microM, and against HIV-2 isolates from 0.00049 to 0.004 microM. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Neither lamivudine nor zidovudine was antagonistic to tested anti-HIV agents, with the exception of stavudine where an antagonistic relationship with zidovudine has been demonstrated in cell culture. See full prescribing information for EPIVIR (lamivudine) and RETROVIR (zidovudine).

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 EC50 value (50% inhibitory concentration) of nevirapine was 90 nM against a panel of 2923 wild-types isolates of HIV-1 that were primarily (93%) clade B clinical isolates from the United States. The 99th percentile EC50 value was 470 nM in this trial. The median EC50 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 O 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. The anti-HIV-1 activity of nevirapine was not antagonistic in combination with the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine, and the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin in cell culture.

Resistance:

Lamivudine and Zidovudine: In subjects receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV 1 isolates from most subjects became phenotypically and genotypically resistant to lamivudine within 12 weeks.

HIV 1 strains resistant to both lamivudine and zidovudine have been isolated from subjects 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 subjects treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated

subjects 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 valine or isoleucine (M184V/I).

Zidovudine: HIV-1 isolates with reduced susceptibility to zidovudine have been selected in cell culture and were also recovered from subjects treated with zidovudine. Genotypic analyses of the isolates selected in cell culture and recovered from zidovudine-treated subjects showed thymidine analogue mutation (TAM) substitutions HIV-1 RT (M41L, D67N, K70R, L210W, T215Y or F, QK219E/R/H/Q/N) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of substitutions. In some subjects harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine.

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

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve subjects receiving either nevirapine (n=24) or nevirapine and zidovudine (n=14) were monitored in Phase 1 and 2 trials ranging from 1 to12 weeks or longer. After 1 week of nevirapine monotherapy, isolates from 3/3 subjects 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 subjects as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the subjects tested (n=24) had HIV-1 isolates with a greater than 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 subjects (80%) had isolates with Y181C substitutions regardless of dose.

Genotypic analysis of isolates from antiretroviral-naïve subjects experiencing virologic failure (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine (trial 2NN) for 48 weeks showed that isolates from 8/25 and 23/46 subjects, 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.

<u>Cross-Resistance:</u>
Lamivudine and Zidovudine: Cross-resistance has been observed among NRTIs. Cross-resistance between lamivudine and zidovudine has not been reported. In some subjects treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a substitution at codon 184, which confers resistance to lamivudine.
TAM substitutions are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, and tenofovir.

Nevirapine: Rapid emergence of HIV-1 strains which are cross-resistant to NNRTIs has been observed in cell culture. Nevirapine-resistant HIV-1 isolates were cross-resistant to the NNRTIs delavirdine, efavirenz and etravirine. The Y188N conferred 22- and 7-fold reductions in susceptibility to delavirdine and efavirenz, respectively, but showed no decrease in susceptibility to etravirine. Similarly, the Y181I substitution reduced susceptibility to delavirdine and etravirine 3-and 8-fold, respectively, but did not reduce susceptibility to efavirenz. However, nevirapine-resistant isolates were susceptible to the NRTIs ddI and ZDV. Similarly, ZDV-resistant isolates were susceptible to nevirapine in cell culture.

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) the human exposures at the recommended dose of 300 mg.

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 per kg per day in mice and 80, 220, and 600 mg per kg per day in rats. The doses in mice were reduced to 20, 30, and 40 mg per kg per day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg per kg per day on day 91 and then to 300 mg per kg per 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.

Nevirapine: Long-term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, 375 or 750 mg per kg per 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 per kg per 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.

Mutagenesis

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic 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 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.

Nevirapine: 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.

Impairment of Fertility

Lamivudine: Lamivudine did not affect male or female fertility in rats at doses up to 4,000 mg per kg per day, associated with concentrations approximately 42 times (male) or 63 times (female) higher than the concentrations (C_{max}) in humans at the dose of 300 mg.

Zidovudine: Zidovudine, administered to male and female rats at doses up to 450 mg per kg per day, which is 7 times the recommended adult dose (300 mg twice daily) based on body surface area, had no effect on fertility based on conception rates.

Nevirapine: 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 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Adults

Lamivudine Plus Zidovudine: The NUCB3007 (CAESAR) study was conducted using lamivudine 150 mg tablets (150 mg twice daily) and zidovudine 100 mg capsules (2 x 100 mg 3 times daily). CAESAR was a multi-center, double-blind, placebo-controlled trial comparing continued current therapy (zidovudine alone [62% of patients] or zidovudine with didanosine or zalcitabine [38% of patients]) to the addition of lamivudine or lamivudine plus an investigational non-nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1,816 HIV-1-infected adults with 25 to 250 (median 122) CD4 cells per mm^3 at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on study was 12 months. Results are summarized in Table 8.

Table 8. Number of Patients (%) with at Least 1 HIV-1 Disease-Progression Event or Death

Endpoint	Current Therapy (n = 460)	Lamivudine plus Current Therapy (n = 896)	Lamivudine plus a NNRTI[a] plus Current Therapy (n = 460)
HIV-1 progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3%)

[a] An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

Nevirapine: Trial BI 1090 was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1 infected subjects with less than 200 $CD4^+$ cells per mm^3 at screening. Initiated in 1995, BI 1090 compared treatment with nevirapine + lamivudine + background therapy versus lamivudine + background therapy in NNRTI-naïve subjects. Treatment doses were nevirapine, 200 mg daily for two weeks followed by 200 mg twice daily or placebo, and lamivudine, 150 mg twice daily. Other antiretroviral agents were given at approved doses. Initial background therapy (in addition to lamivudine) was one NRTI in 1309 subjects (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%). The subjects (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV-1 infection, with a median baseline $CD4^+$ cell count of 96 cells per mm^3 and a baseline HIV-1 RNA of 4.58 log_{10} copies per mL (38,291 copies per mL). Prior to entering the trial, 45% had previously experienced an AIDS-defining clinical event. Eighty-nine percent had antiretroviral treatment prior to entering the trial. BI 1090 was originally designed as a clinical endpoint trial. Prior to unblinding the trial, the primary endpoint was changed to proportion of subjects with HIV-1 RNA less than 50 copies/mL and not previously failed at 48 weeks. Treatment response and outcomes are shown in Table 9.

Table 9 BI 1090 Outcomes Through 48 Weeks

Outcome	Nevirapine (N=1121) %	Placebo (N=1128) %

Responders at 48 weeks: HIV-1 RNA <50 copies/mL	18		2	
Treatment Failure	82		98	
Never suppressed viral load		45		66
Virologic failure after response		7		4
CDC category C event or death		10		11
Added antiretroviral therapy[1] while <50 copies/mL		5		1
Discontinued trial therapy due to AE		7		6
Discontinued trial <48 weeks[2]		9		10

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

The change from baseline in $CD4^+$ cell count through one year of therapy was significantly greater for the nevirapine group compared to the placebo group for the overall trial population (64 cells per mm^3 vs 22 cells per mm^3, respectively), as well as for subjects who entered the trial as treatment-naïve or having received only ZDV (85 cells per mm^3 vs 25 cells per mm^3, respectively).

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

Trial BI 1046 (INCAS) was a double-blind, placebo-controlled, randomized, three-arm trial with 151 HIV-1 infected subjects with $CD4^+$ cell counts of 200 to 600 cells/mm^3 at baseline. BI 1046 compared treatment with nevirapine +zidovudine+didanosine to nevirapine +zidovudine and zidovudine+didanosine. Treatment doses were nevirapine at 200 mg daily for two weeks followed by 200 mg twice daily or placebo, zidovudine at 200 mg three times daily, and didanosine at 125 or 200 mg twice daily (depending on body weight). The subjects had mean baseline HIV-1 RNA of 4.41 $\log_{10}$ copies per mL (25,704 copies per mL) and mean baseline $CD4^+$ cell count of 376 cells per mm^3. The primary endpoint was the proportion of subjects with HIV-1 RNA less than 400 copies per mL and not previously failed at 48 weeks. The virologic responder rates at 48 weeks were 45% for subjects treated with nevirapine+zidovudine+didanosine, 19% for subjects treated with zidovudine+didanosine, and 0% for subjects treated with nevirapine+zidovudine.

$CD4^+$ cell counts in the nevirapine+ZDV+ddI group increased above baseline by a mean of 139 cells per mm^3 at one year, significantly greater than the increase of 87 cells per mm^3 in the ZDV+ddI subjects. The nevirapine+ZDV group mean decreased by 6 cells per mm^3 below baseline.

14.2 Pediatric Patients

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 per m^2) and weight-based dosing (4 or 7 mg per kg)] in combination with zidovudine and lamivudine. 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 per mL and a median baseline CD4+ cell count of 527 cells per mm^3 (range 37-2279). One hundred and five (85%) completed the 48-week period while 18 (15%) discontinued prematurely. Of the subjects 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 per mL at 48 weeks was 47% (58/123).

16 HOW SUPPLIED/STORAGE AND HANDLING

Lamivudine, nevirapine, and zidovudine tablets contain 150 mg of lamivudine, 200 mg of nevirapine, and 300 mg of zidovudine. The tablets are white to off-white colored, capsule shaped, bevelled edged, biconvex, film-coated, debossed with “I” on one side and “47” on other side. They are available as follows.

Bottles of 60 with induction seal and child-resistant closure NDC 42571-166-60

Storage:

Store below 30°C (86°F). Store in tight, light-resistant containers.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

Hepatotoxicity and Skin Reactions

Inform patients of the possibility of severe liver disease or skin reactions associated with nevirapine that may result in death. Instruct patients developing signs or symptoms of liver disease or severe skin reactions to discontinue lamivudine, nevirapine, and zidovudine tablets and seek medical attention immediately, including performance of laboratory monitoring. Symptoms of liver disease include fatigue, malaise, anorexia, nausea, jaundice, acholic stools, liver tenderness or hepatomegaly. Symptoms of severe skin or hypersensitivity reactions include rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis.

Intensive clinical and laboratory monitoring, including liver enzymes, is essential during the first 18 weeks of therapy with lamivudine, nevirapine, and zidovudine tablets to detect potentially

life-threatening hepatotoxicity and skin reactions. However, liver disease can occur after this period; therefore, monitoring should continue at frequent intervals throughout lamivudine, nevirapine, and zidovudine tablets treatment. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of hepatic events. Advise patients with signs and symptoms of hepatitis to discontinue lamivudine, nevirapine, and zidovudine tablets and seek medical evaluation immediately. If a lamivudine, nevirapine, and zidovudine tablets is discontinued due to hepatotoxicity, do not restart it. Patients, particularly women, with increased $CD4^+$ cell count at initiation of lamivudine, nevirapine, and zidovudine tablets therapy (greater than 250 cells/mm^3 in women and greater than 400 cells/mm^3 in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Advise patients that co-infection with hepatitis B or C and/or increased transaminases at the start of therapy with lamivudine, nevirapine, and zidovudine tablets are associated with a greater risk of later symptomatic events (6 weeks or more after starting lamivudine, nevirapine, and zidovudine tablets) and asymptomatic increases in AST or ALT [*see Warnings and Precautions (5.1)*].

The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. Instruct patients that if any rash occurs during the two-week lead-in period, do not escalate the lamivudine, nevirapine, and zidovudine tablets dose until the rash resolves. The total duration of the once-daily lead-in dosing period should not exceed 28 days, at which point an alternative regimen may need to be started. Any patient experiencing a rash should have their liver enzymes (AST, ALT) evaluated immediately. Patients with severe rash or hypersensitivity reactions should discontinue lamivudine, nevirapine, and zidovudine tablets immediately and consult a physician. Lamivudine, nevirapine, and zidovudine tablets should not be restarted following severe skin rash or hypersensitivity reaction. Women tend to be at higher risk for development of lamivudine, nevirapine, and zidovudine tablets-associated rash [*see Warnings and Precautions (5.2)*].

Neutropenia and Anemia

Inform patients that the important toxicities associated with zidovudine are neutropenia and/or anemia. Inform them of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV-1 disease *[see Boxed Warning, Warnings and Precautions (5.3)]*.

Myopathy: Inform patients that myopathy and myositis with pathological changes, similar to that produced by HIV-1 disease, have been associated with prolonged use of zidovudine *[see Warnings and Precautions (5.4)]*.

Lactic Acidosis/Hepatomegaly: Advise patients that lactic acidosis and severe hepatomegaly with steatosis have been reported with use of nucleoside analogues and other antiretrovirals. Advise patients to stop taking lamivudine, nevirapine, and zidovudine tablets if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Patients with Hepatitis B or C Co-infection: Advise patients co infected with HIV 1 and HBV that worsening of liver disease has occurred in some cases when treatment with lamivudine was

discontinued. Advise patients to discuss any changes in regimen with their healthcare provider *[see Warnings and Precautions (5.6)]*.

Inform patients with HIV 1/HCV co-infection that 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 (5.7)]*.

Drug Interactions: Advise patients that other medications may interact with lamivudine, nevirapine, and zidovudine tablets and certain medications, including ganciclovir, interferon alfa, and ribavirin, may exacerbate the toxicity of zidovudine, a component of lamivudine, nevirapine, and zidovudine tablets *[see Drug Interactions (7)]*.

Advise patients to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort *[see Warnings and Precautions (5.10) and Drug Interactions (7)]*.
Immune Reconstitution Syndrome: Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when lamivudine, nevirapine, and zidovudine tablets is started *[see Warnings and Precautions (5.12)]*.

Lipoatrophy: Advise patients that loss of subcutaneous fat may occur in patients receiving lamivudine, nevirapine, and zidovudine tablets and that they will be regularly assessed during therapy *[see Warnings and Precautions (5.9)]*.

Lactation: Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Missed Dose: Instruct patients that if they miss a dose of lamivudine, nevirapine, and zidovudine tablets, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose *[see Dosage and Administration (2)]*.

Infertility: Advise females of reproductive potential of the potential for impaired fertility from nevirapine *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*

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Manufactured for:
Micro Labs USA Inc.
Basking Ridge, NJ 07920

MEDICATION GUIDE
lamivudine, nevirapine, and
zidovudine tablets,
150 mg/200 mg/300 mg

What is the most important information I should know about lamivudine, nevirapine, and zidovudine tablets?

Lamivudine, nevirapine, and zidovudine tablets can cause severe liver and skin problems that may lead to death. These problems can happen at any time during treatment, but your risk is higher during the first 18 weeks of treatment.

Lamivudine, nevirapine, and zidovudine tablets can cause serious side effects, including:

- **Severe liver problems.** Some people taking lamivudine, nevirapine, and zidovudine tablets and other nevirapine-containing products may develop severe liver problems that can lead to liver failure and the need for a liver transplant, or death. Your liver may become enlarge (hepatomegaly) and you may develop fat in your liver (steatosis). If you have liver problems, you may get a rash.
  - Women have a higher risk of developing liver problems during treatment with lamivudine, nevirapine, and zidovudine tablets than men.
  - People who have abnormal liver test results before starting lamivudine, nevirapine, and zidovudine tablets and people with hepatitis B or C also have a greater risk of getting liver problems.

  People who have higher $CD4^+$ cell counts when they begin lamivudine, nevirapine, and zidovudine tablets have a higher risk of liver problems, especially:
  - Women with $CD4^+$ counts higher than 250 cells/mm^3. This group has the highest risk.
  - Men with $CD4^+$ counts higher than 400 cells/mm^3.

  Stop taking lamivudine, nevirapine, and zidovudine tablets and call your healthcare provider right away if you have any of the following symptoms of liver problems with or without a skin rash:
  - dark (tea colored) urine
  - light-colored bowel movements (stools)
  - feeling sick to your stomach (nausea)
  - pain or tenderness on your right side below your ribs
  - loss of appetite
  - yellowing of your skin or whites of your eyes
  - fever
  - feel unwell or like you have the flu
  - tiredness
- **Severe skin reactions and rash**. Some skin reactions and rashes may be severe, life-threatening, and in some people, may lead to death. Most severe skin reactions and rashes happen in the first 6 weeks of treatment with lamivudine, nevirapine, and zidovudine tablets.
  - Women have a higher risk of developing a rash during treatment with lamivudine, nevirapine, and zidovudine tablets than men.

  Stop taking lamivudine, nevirapine, and zidovudine tablets and call your healthcare provider right away if you get a rash with any of the following symptoms:
  - blisters
  - red or inflamed eyes, like “pink eye” (conjunctivitis)
  - swelling of your face
  - feel unwell or like you have the flu
  - muscle or joint aches
  - mouth sores
  - fever
  - tiredness
- Your healthcare provider should do blood tests often to check your liver function and check for severe skin reactions during the first 18 weeks of treatment with lamivudine, nevirapine, and zidovudine tablets. You should continue to see your healthcare provider and have your liver checked regularly during your treatment with lamivudine, nevirapine, and zidovudine tablets. It is important for you to keep all of your healthcare provider appointments.
- **If your healthcare provider tells you to stop treatment with lamivudine, nevirapine, and zidovudine tablets because you have had any of the severe liver or skin symptoms listed above, you should never take lamivudine, nevirapine, and zidovudine tablets again.**
- **Blood problems**. Zidovudine, one of the medicines in lamivudine, nevirapine, and zidovudine tablets, can cause serious blood cell problems. These include reduced numbers of white blood cells (neutropenia) and extremely reduced numbers of red blood cells (anemia). These blood cell problems are especially likely to happen in people with advanced HIV-1 disease or AIDS. Your healthcare provider should check your blood cell counts regularly during treatment with lamivudine, nevirapine, and zidovudine tablets.
- **Muscle pain or weakness (myopathy)** can happen during treatment with lamivudine, nevirapine, and zidovudine tablets. Zidovudine, one of the medicines in lamivudine, nevirapine, and zidovudine tablets, can cause muscle pain or weakness when used for a long time.
- **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take lamivudine, nevirapine, and zidovudine tablets. Lactic acidosis is a serious medical emergency that can cause death.

Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:

- o feel very weak or tired
- o unusual (not normal) muscle pain
- o trouble breathing
- o stomach pain with nausea and vomiting
- o feel cold, especially in your arms and legs
- o feel dizzy or light-headed
- o have a fast or irregular heartbeat

You may be more likely to get lactic acid or severe liver problems if you are female, are very overweight (obese), or have been taking nucleoside analogue medicines for a long time.

- **Worsening of hepatitis B virus in people who have HIV-1 infection.** If you have HIV-1 and hepatitis B virus (HBV) infection, your HBV may get worse (flare-up) if you stop taking lamivudine, nevirapine, and zidovudine tablets. A "flare-up" is when your HBV infection suddenly returns in a worse way than before. Worsening liver disease is serious and may lead to death.
  - o Do not run out of lamivudine, nevirapine, and zidovudine tablets. Refill your prescription or talk to your healthcare provider before your lamivudine, nevirapine, and zidovudine tablets is all gone.
  - o Do not stop lamivudine, nevirapine, and zidovudine tablets without first talking to your healthcare provider.
  - o If you stop taking lamivudine, nevirapine, and zidovudine tablets, your healthcare provider will need to check your health often and do blood test regularly for several months to check your liver.
- **Resistant Hepatitis B Virus (HBV)**. If you have HIV-1 and hepatitis B, the hepatitis B virus can change (mutate) during your treatment with lamivudine, nevirapine, and zidovudine tablets and become harder to treat (resistant).

See "What are the possible side effects of lamivudine, nevirapine, and zidovudine tablets?" for more information about side effects.

What is lamivudine, nevirapine, and zidovudine tablets?

Lamivudine, nevirapine, and zidovudine tablets is a prescription HIV-1 medicine used alone or with other antiretroviral medicines to treat Human Immunodeficiency Virus 1 (HIV-1) in adults and in children weighing at least 77 pounds (35 kg). HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

Lamivudine, nevirapine, and zidovudine tablets contains the prescription medicines lamivudine, nevirapine, and zidovudine.

- If you are a woman with $CD4^+$ counts higher than 250 cells per mm^3 or a man with $CD4^+$ counts higher than 400 cells per mm^3, you and your healthcare provider will decide if starting lamivudine, nevirapine, and zidovudine tablets is right for you.
- Lamivudine, nevirapine, and zidovudine tablets is not recommended for use in children who weigh less than 77 pounds (35 kg).

Do not take lamivudine, nevirapine, and zidovudine tablets:

- if you are allergic to any of the ingredients in lamivudine, nevirapine, and zidovudine. See the end of this Medication Guide for a complete list of ingredients in lamivudine, nevirapine, and zidovudine tablets.
- if you have liver problems.
- as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens. Lamivudine, nevirapine, and zidovudine tablets is only for people diagnosed with HIV-1. If you have not been diagnosed as HIV positive, then do not take lamivudine, nevirapine, and zidovudine tablets.

Before taking lamivudine, nevirapine, and zidovudine tablets, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had hepatitis (inflammation of your liver) or problems with your liver. See **"What is the most important information I should know about lamivudine, nevirapine, and zidovudine tablets?"**
- have a history of pancreatitis (Inflammation of your pancreas)
- have kidney problems
- have trouble swallowing pills
- are pregnant or plan to become pregnant. It is not known if lamivudine, nevirapine, and zidovudine tablets will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Lamivudine, nevirapine, and zidovudine tablets can pass into your breast milk and may harm your baby. You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Do not breastfeed during treatment with lamivudine, nevirapine, and zidovudine tablets. Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. **Especially tell your healthcare provider if you take St. John's wort.**

- Some medicines interact with lamivudine, nevirapine, and zidovudine tablets. Keep a list of your medicines to show your healthcare provider or pharmacist.
- You can ask your healthcare provider or pharmacist for a list of medicines that interact with lamivudine, nevirapine, and zidovudine tablets.

- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take lamivudine, nevirapine, and zidovudine tablets with other medicines.

How should I take lamivudine, nevirapine, and zidovudine tablets?

- **Take lamivudine, nevirapine, and zidovudine tablets exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.**
- Lamivudine, nevirapine, and zidovudine tablets may be taken in combination with other antiretroviral medicines.
- You should not take more than 1 form of lamivudine, nevirapine, and zidovudine medicine at the same time. Talk to your healthcare provider if you have any questions.
- Lamivudine, nevirapine, and zidovudine tablets can be taken with or without food.
- Do not miss a dose of lamivudine, nevirapine, and zidovudine tablets. If you miss a dose of lamivudine, nevirapine, and zidovudine tablets, take the missed dose as soon as you remember. If it is almost time for your next dose, do not take the missed dose. You should take the next dose at your regular time. Do not take 2 doses at the same time.
- If you stop taking lamivudine, nevirapine, and zidovudine tablets for more than 7 days, ask your healthcare provider how much to take before you start taking it again. You may need to begin taking the lamivudine, nevirapine, and zidovudine tablets starting dose again, which is taken 1 time each day for 14 days.
- If you take too much lamivudine, nevirapine, and zidovudine tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

Starting lamivudine, nevirapine, and zidovudine tablets:

1. Your healthcare provider should start you with 1 dose each day to lower your chance of getting a serious rash. **It is important that you only take 1 dose of lamivudine, nevirapine, and zidovudine tablets each day for the first 14 days. In addition, you will need to take a dose of other HIV medicines 12 hours after your lamivudine, nevirapine, and zidovudine tablets for the first 14 days.**
   - **Call your healthcare provider right away if you get a skin rash during the first 14 days of lamivudine, nevirapine, and zidovudine tablets treatment**.
   - **Do not increase your dose to 2 times a day if you have a rash.**
   - You should never take your starting dose for longer than 28 days. If after 28 days you are still receiving this starting dose because you have a rash, you and your healthcare provider should talk about prescribing another HIV-1 medicine for you instead of lamivudine, nevirapine, and zidovudine tablets.
2. Day 15, you will take 1 lamivudine, nevirapine, and zidovudine tablet 2 times a day.

What are the possible side effects of lamivudine, nevirapine, and zidovudine tablets?

Lamivudine, nevirapine, and zidovudine tablets may cause serious side effects, including:

See "**What is the most important information I should know about lamivudine, nevirapine, and zidovudine tablets**"

- **Use with interferon and ribavirin-based regimens**. Worsening of liver disease that has caused death has happened in people infected with both HIV-1 and hepatitis C virus who are taking antiretroviral medicines, and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking lamivudine, nevirapine, and zidovudine tablets and interferon with or without ribavirin, tell your healthcare provider if you have any new symptoms.
- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with lamivudine, nevirapine, and zidovudine tablets if they:
  - have taken nucleoside analogue medicines in the past
  - have a history of pancreatitis
  - have other risks for pancreatitis

Call your healthcare provider right away if your child develops signs of symptoms of pancreatitis including severe upper stomach-area pain, with or without nausea and vomiting. Your healthcare provider may tell you to stop giving lamivudine, nevirapine, and zidovudine tablets to your child if their symptoms and blood test results show that your child may have pancreatitis.

- **Loss of body fat** can happen in people who take HIV-1 medicines that contain zidovudine. The loss of fat may occur in the legs, arms, buttocks, and face. The loss of fat may be permanent and long-term health effects are not known.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.

The most common side effects of lamivudine and zidovudine are:

- headache
- nasal signs and symptoms
- diarrhea

- nausea
- not feeling well and tiredness
- cough

The most common side effect of nevirapine is rash.

Lamivudine, nevirapine, and zidovudine tablets may cause decreased fertility in females. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of lamivudine, nevirapine, and zidovudine tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store lamivudine, nevirapine, and zidovudine tablets?

- Store lamivudine, nevirapine, and zidovudine tablets below 86°F (30°C).
- Store tablets in a tightly closed container that is protected from light.

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

General information about the safe and effective use of lamivudine, nevirapine, and zidovudine tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use lamivudine, nevirapine, and zidovudine tablets for a condition for which it was not prescribed. Do not give lamivudine, nevirapine, and zidovudine tablets to other people, even if they have the same condition you have. It may harm them. You can ask your pharmacist or healthcare provider for information about lamivudine, nevirapine, and zidovudine tablets that is written for health professionals.

What are the ingredients in lamivudine, nevirapine, and zidovudine tablets?

Active ingredients: lamivudine, nevirapine, and zidovudine.
Inactive ingredients: colloidal silicon dioxide, hydroxy propyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone k-25, and sodium starch glycolate.
The tablets are coated with opadry white 13b58894, that is made of hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

Manufactured by: Micro Labs Limited, Goa-403 722, INDIA.
Manufactured for: **Micro Labs USA Inc.**

For more information, call 1-855-839-8195.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: Month/2018

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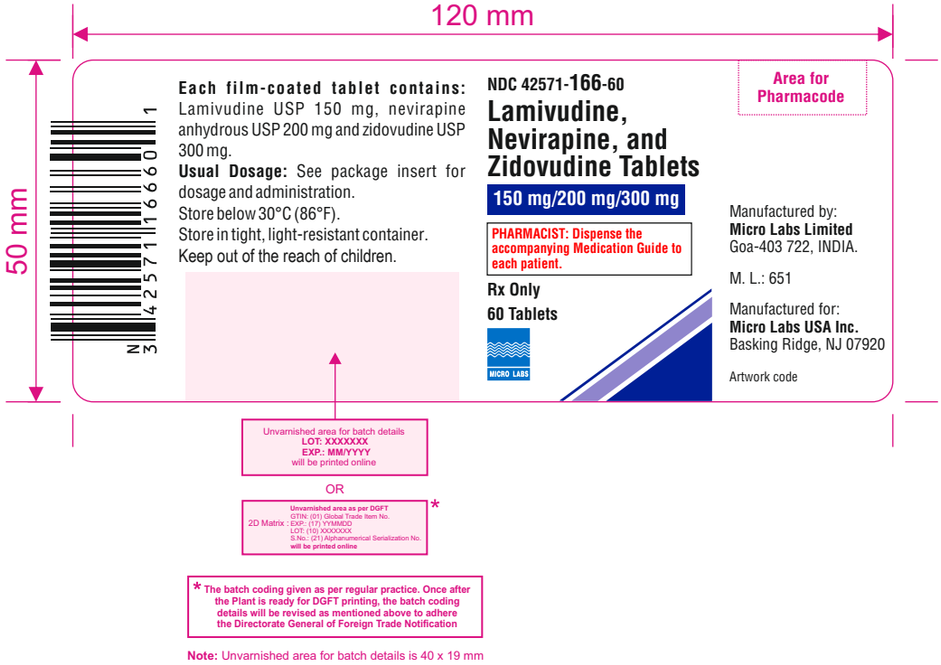

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