

## 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 150 mg/200 mg/300 mg

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

See full prescribing information for complete boxed warning.

- Hematologic toxicity including neutropenia and anemia have been associated with the use of zidovudine, one of the components of lamivudine/zidovudine tablet (5.1)
- Symptomatic myopathy associated with prolonged use of zidovudine. (5.2)
- Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including zidovudine. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.3)
- 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/zidovudine tablet. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.4)
- Fatal and non-fatal hepatotoxicity (5.10)
- Fatal and non-fatal skin reactions (5.11)

#### Discontinue immediately if experiencing:

- Signs or symptoms of hepatitis (5.10)
- Increased transaminases combined with rash or other systemic symptoms (5.1)
- Severe skin or hypersensitivity reactions (5.11)
- Any rash with systemic symptoms (5.11)

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

## .....INDICATIONS AND USAGE.....

Lamivudine, Nevirapine, and Zidovudine Tablet, a combination of two nucleoside analogue reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor, is indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

#### Important Considerations:

- Initiation of treatment is not recommended in the following populations unless the benefits outweigh the risks (1, 5.1)
  - adult females with CD4<sup>+</sup> cell counts greater than 250 cells/mm<sup>3</sup>
  - adult males with CD4<sup>+</sup> cell counts greater than 400 cells/mm<sup>3</sup>
- The 14-day lead-in period must be strictly followed; it has been demonstrated to reduce the frequency of rash (2.4, 5.2)

## .....DOSAGE AND ADMINISTRATION.....

Adults and Adolescents weighing  $\geq 30$  kg:

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

One Lamivudine, Nevirapine, and Zidovudine Tablet (containing 150 mg of lamivudine, 200 mg of nevirapine, and 300 mg of zidovudine) taken once daily orally followed by a daily oral dose of lamivudine 150 mg and zidovudine 300 mg 12 hours later.

Maintenance:

One Lamivudine, Nevirapine, and Zidovudine Tablet (containing 150 mg of lamivudine, 200 mg of nevirapine, and 300 mg of zidovudine) taken twice daily orally.

Lamivudine, Nevirapine, and Zidovudine Tablet should be taken on an empty stomach.

## .....DOSAGE FORMS AND STRENGTHS.....

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

## .....CONTRAINDICATIONS.....

- Lamivudine, Nevirapine and Zidovudine Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis, Stevens-Johnson syndrome). (4)
- Patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment (4, 5.10)
- Use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens, an unapproved use (4, 5.10)

## .....WARNINGS AND PRECAUTIONS.....

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

## .....ADVERSE REACTIONS.....

- Most commonly reported adverse reactions were rash, headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact **Macleods Pharmaceuticals Limited at 314-814-2833 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

## .....DRUG INTERACTIONS.....

- Concomitant use with the following drugs should be avoided: stavudine (7.1), zalcitabine (7.1), doxorubicin (7.2).
- Bone marrow suppressive/cytotoxic agents: May increase the hematologic toxicity of zidovudine. (7.3)

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 (5.4,7, 12.3)

## .....USE IN SPECIFIC POPULATIONS.....

- Nursing Mothers: HIV-1 infected mothers in the United States should not breastfeed to avoid potential postnatal transmission of HIV-1. (8.3)
- 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.

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## FULL PRESCRIBING INFORMATION

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

**Hematologic Toxicity:** Zidovudine, one of the active ingredients in Lamivudine, Nevirapine, and Zidovudine Tablets, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease [*see Warnings and Precautions (5.1)*].

**Myopathy:** Prolonged use of zidovudine has been associated with symptomatic myopathy [*see Warnings and Precautions (5.2)*].

**Lactic Acidosis and Severe Hepatomegaly:** Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine, and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur [*see Warnings and Precautions (5.3)*].

**Exacerbations of Hepatitis B:** Severe, acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine, which is one component of Lamivudine, Nevirapine, and Zidovudine Tablets. 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 Tablets and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted [*see Warnings and Precautions (5.4)*].

### **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<sup>+</sup> cell counts at initiation of therapy place patients at increased risk; women with CD4<sup>+</sup> cell counts greater than 250 cells/mm<sup>3</sup>, including pregnant women receiving nevirapine in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk. However, hepatotoxicity associated with nevirapine use can occur in both genders, all CD4<sup>+</sup> 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*]. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue Lamivudine, Nevirapine, and Zidovudine Tablets 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, a component of Lamivudine, Nevirapine, and Zidovudine Tablets. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. Transaminase levels should be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. The 14-day lead-in period with nevirapine 200 mg daily dosing has been observed to decrease the incidence of rash and must be followed [*see Warnings and Precautions (5.2)*].

**MONITORING:**

Patients must be monitored intensively during the first 18 weeks of therapy with nevirapine to detect potentially life-threatening hepatotoxicity or skin reactions. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart nevirapine following 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.

**1 INDICATIONS AND USAGE**

Lamivudine, Nevirapine and Zidovudine Tablets, a combination of two nucleoside analogue reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor, are indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Additional important information 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, nevirapine should not be initiated in adult females with CD4<sup>+</sup> cell counts greater than 250 cells/mm<sup>3</sup> or in adult males with CD4<sup>+</sup> cell counts greater than 400 cells/mm<sup>3</sup> unless the benefit outweighs the risk [*see Boxed Warning and Warnings and Precautions (5.1)*].
- The 14-day lead-in period with nevirapine 200 mg daily dosing must be strictly followed; it has been demonstrated to reduce the frequency of rash [*see Dosage and Administration (2.4) and Warnings and Precautions (5.2)*].
- If rash persists beyond the 14-day lead-in period, do not dose escalate to 200 mg twice daily. The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point an alternative regimen should be sought.

**2 DOSAGE AND ADMINISTRATION****2.1 Adults and Adolescents Weighing ≥30 kg**

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

One Lamivudine, Nevirapine, and Zidovudine Tablet (containing 150 mg of lamivudine, 200 mg of nevirapine, and 300 mg of zidovudine) taken once daily orally followed by a daily oral dose of lamivudine 150 mg and zidovudine 300 mg 12 hours later.

Maintenance:

If the initial 14 days of dosing is tolerated without any incidence of rash, the recommended maintenance dose is:

One Lamivudine, Nevirapine, and Zidovudine Tablet (containing 150 mg of lamivudine, 200 mg of nevirapine, and 300 mg of zidovudine) taken twice daily orally.

Lamivudine, Nevirapine, and Zidovudine Tablets should be taken on an empty stomach.

## 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. The optimal frequency of monitoring during this period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver enzyme tests at baseline, prior to dose escalation, and at two weeks post-dose escalation. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout 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 tablet, it should not be prescribed for pediatric patients weighing less than 30 kg or patients requiring dosage adjustment, such as those with reduced renal function (creatinine clearance less than 50 mL/min), patients with hepatic impairment, or patients experiencing dose-limiting adverse reactions. Liquid and solid oral formulations of the individual components of lamivudine, nevirapine and zidovudine 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 boxed warnings, warnings and precautions (5.2) and patient counseling information (17.1)*]. 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/day (150 mg/m<sup>2</sup>/day in pediatric patients) until the rash has resolved [*see Warnings and Precautions (5.2) and patient counseling information (17.1)*].**

### *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 Tablets using the Lead-in Period dosing for 14 days.

### **3 DOSAGE FORMS AND STRENGTHS**

Lamivudine, Nevirapine, and Zidovudine Tablets are white colored, oval shaped film coated biconvex tablets having 'ML' and '20' debossed on one side of the tablet and having plain surface on other side. Tablets: Lamivudine 150mg, Nevirapine 200 mg and Zidovudine 300mg

### **4 CONTRAINDICATIONS**

Lamivudine, Nevirapine, and Zidovudine Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis, Stevens-Johnson syndrome), moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment to any of the components of the product and for use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.7)*].

### **5 WARNINGS AND PRECAUTIONS**

#### **Lamivudine and Zidovudine**

#### **5.1 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/mm<sup>3</sup> or hemoglobin less than 9.5 g/dL [see *Adverse Reactions (6.1)*].

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

#### **5.2 Myopathy**

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

#### **5.3 Lactic Acidosis/Hepatomegaly With Steatosis**

Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine, and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering Lamivudine, Nevirapine and Zidovudine Tablets to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Lamivudine, 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).

#### **5.4 Patients With HIV-1 and Hepatitis B Virus Co-infection**

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-1-infected patients

treated with lamivudine, a component of Lamivudine, Nevirapine and Zidovudine Tablets, for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence hepatitis B viral DNA (HBV DNA). Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

Important Differences Among Lamivudine-Containing Products: Lamivudine, Nevirapine and Zidovudine Tablets contain a higher dose of the same active ingredient (lamivudine) than EPIVIR-HBV<sup>®</sup> (lamivudine) tablets and oral solution. EPIVIR-HBV was developed for treating chronic hepatitis B. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

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

## **5.5 Use With Other, Lamivudine-, Zidovudine-, and/or Emtricitabine-Containing Products**

Lamivudine, Nevirapine, and Zidovudine Tablets are a fixed-dose combination of lamivudine, nevirapine, and zidovudine. Lamivudine, Nevirapine and Zidovudine Tablets should not be administered concomitantly with other lamivudine- or zidovudine-containing products including lamivudine tablets and oral solution, EPIVIR- HBV tablets and oral solution, zidovudine tablets, capsules, syrup, and IV Infusion, EPZICOM<sup>®</sup> (abacavir sulfate and lamivudine) tablets, or TRIZIVIR<sup>®</sup> (abacavir sulfate, lamivudine, and zidovudine) tablets; or emtricitabine-containing products, including ATRIPLA<sup>®</sup> (efavirenz, emtricitabine, and tenofovir), EMTRIVA<sup>®</sup> (emtricitabine), or TRUVADA<sup>®</sup> (emtricitabine and tenofovir) or COMPLERA<sup>®</sup> (rilpivirine/emtricitabine/tenofovir).

## **5.6 Use With Interferon- and Ribavirin-Based Regimens**

*In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co administered with lamivudine or zidovudine in HIV-1/HCV co-infected patients [see *Clinical Pharmacology (12.3)*], hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and Lamivudine, Nevirapine and Zidovudine Tablets should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. 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., Childs Pugh greater than 6) (see the complete prescribing information for interferon and ribavirin).

Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Co-administration of ribavirin and zidovudine is not advised.

## 5.7 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)*].

## 5.8 Immune Reconstitution Syndrome

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

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

## 5.9 Fat Redistribution

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

## Nevirapine

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

**The first 18 weeks of therapy with nevirapine are a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life-threatening hepatic events and skin reactions.** The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, 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. In addition, the

14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the

frequency of rash [*see Dosage and Administration (2.1)*].

### **5.10 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, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately half of the patients with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use. Patients with signs or symptoms of hepatitis must be advised to discontinue Lamivudine, Nevirapine, and Zidovudine Tablets and immediately seek medical evaluation, which should include liver enzyme tests.

**Transaminases should be checked immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Transaminases should also be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if transaminases are initially normal or alternative diagnoses are possible [*see Boxed Warning, Dosage and Administration (2.3), and Patient Counseling Information (17.1)*].**

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<sup>+</sup> 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<sup>+</sup> cell counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4<sup>+</sup> cell counts greater than 250 cells/mm<sup>3</sup> had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with CD4<sup>+</sup> cell counts less than 250 cells/mm<sup>3</sup> (11% versus 1%). An increased risk was observed in men with CD4<sup>+</sup> cell counts greater than 400 cells/mm<sup>3</sup> (6% versus 1% for men with CD4<sup>+</sup> cell counts less than 400 cells/mm<sup>3</sup>). However, all patients, regardless of gender, CD4<sup>+</sup>

cell count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4<sup>+</sup> 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 (4.1)*, *Use in Specific Populations (8.7)*, and *Clinical Pharmacology (12.3)*].

### **5.11 Skin Reactions**

Severe and life-threatening skin reactions, including fatal cases, have been reported, occurring most frequently during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction including hepatic failure. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use. In controlled clinical trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 2% of nevirapine recipients compared to less than 1% of placebo subjects.

Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue nevirapine and seek medical evaluation immediately [*see Boxed Warning and Patient Counseling Information (17.1)*]. Do not restart nevirapine following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

If patients present with a suspected nevirapine-associated rash, 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 Lamivudine, Nevirapine, and Zidovudine Tablets must be initiated with a 14-day lead-in period of 200 mg/day, 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 nevirapine dose to a patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg/day 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 (2.4)*]. 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/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.

### **5.12 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 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. Co-administration of nevirapine and efavirenz is not recommended as this combination has been associated with an increase in adverse reactions and no improvement in efficacy.

### **5.13 Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including 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 jiroveci* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

### **5.14 Fat Redistribution**

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

## **6 ADVERSE REACTIONS**

### **Lamivudine and Zidovudine**

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 (5.1)*].
- Symptomatic myopathy [*see Boxed Warning, Warnings and Precautions (5.2)*].
- Lactic acidosis and hepatomegaly with steatosis [*see Boxed Warning, Warnings and Precautions (5.3)*].
- Acute exacerbations of hepatitis B [*see Boxed Warning, Warnings and Precautions (5.4)*].
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C [*see Warnings and Precautions (5.6)*].
- Exacerbation of anemia in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine [*see Warnings and Precautions (5.6)*].
- Pancreatitis [*see Warnings and Precautions (5.7)*].

## 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 Plus Zidovudine Administered As Separate Formulations: In 4 randomized, controlled trials of lamivudine tablet 300 mg per day plus zidovudine tablet 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 ( $\geq 5\%$  Frequency) in 4 Controlled Clinical Trials With lamivudine tablet 300 mg/day and zidovudine tablet 600 mg/day**

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

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received lamivudine tablet in controlled clinical trials [see *Warnings and Precautions (5.7)*].

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 tablet 300 mg/day plus zidovudine tablet 600 mg/day\***

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

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

n = Number of patients assessed.

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

## 6.2 Postmarketing Experience

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

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 (5.3), (5.4), (5.7)*].

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**

### **6.3 Clinical Trials in Adults**

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

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<sup>+</sup> cell counts (greater than 250 cells/mm<sup>3</sup> in women and greater than 400 cells/mm<sup>3</sup> 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 <sup>1</sup>		Trials 1037, 1038, 1046 <sup>2</sup>	
	Nevirapine (n=1121)	Placebo (n=1128)	Nevirapine (n=253)	Placebo (n=203)
Median exposure (weeks)	58	52	28	28
Any adverse event	15%	11%	32%	13%
Rash	5	2	7	2
Nausea	1	1	8	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

<sup>1</sup> Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had CD4<sup>+</sup> cell counts less than 200 cells/mm<sup>3</sup>.

<sup>2</sup> Background therapy included ZDV and ZDV+ddI; nevirapine monotherapy was administered in some subjects. Subjects had CD4<sup>+</sup> cell count greater than or equal to 200 cells/mm<sup>3</sup>.

*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**

Laboratory Abnormality	Trial 1090 <sup>1</sup>		Trials 1037, 1038, 1046 <sup>2</sup>	
	Nevirapine (n=1121)	Placebo (n=1128)	Nevirapine (n=253)	Placebo (n=203)
<b>Blood Chemistry</b>				
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
<b>Hematology</b>				
Hemoglobin <8.0 g/dL	3	4	0	0
Platelets <50,000/mm <sup>3</sup>	1	1	<1	2
Neutrophils <750/mm <sup>3</sup>	13	14	4	1

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

<sup>2</sup>Background therapy included ZDV and ZDV+ddI; Nevirapine monotherapy was administered in some patients. Patients had CD4<sup>+</sup> cell count ≥200 cells/mm<sup>3</sup>.

## 6.4 Post-Marketing Experience

In addition to the adverse events identified during clinical trials, the following adverse reactions have been identified during post-approval use of nevirapine. 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:* fever, somnolence, drug withdrawal [*see Drug Interactions (7)*], redistribution/accumulation of body fat [*see Warnings and Precautions (5.6)*]

*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 [*see Warnings and Precautions (5.1)*] plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and/or renal dysfunction have been reported.

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

## 7 DRUG INTERACTIONS

### Lamivudine and Zidovudine

No drug interaction studies have been conducted using lamivudine/zidovudine fixed dose combination tablets [*see Clinical Pharmacology (12.3)*].

#### 7.1 Zidovudine and Antiretroviral Agents

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

*Nucleoside Analogues Affecting DNA Replication:* Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the *in vitro* antiviral activity of zidovudine against HIV-1; concomitant use of such drugs should be avoided.

#### 7.2 Zidovudine and Doxorubicin

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

#### 7.3 Zidovudine and Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

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

#### 7.4 Lamivudine and Interferon- and Ribavirin-Based Regimens

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-

1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin [see *Warnings and Precautions (5.5), Clinical Pharmacology (12.3)*].

### 7.5 Lamivudine and Trimethoprim/Sulfamethoxazole (TMP/SMX)

No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

### 7.6 Drug interactions with Nevirapine

Nevirapine, a component of Lamivudine, Nevirapine, and Zidovudine Tablets, 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 8. Clinical comments about possible dosage modifications based on established drug interactions are listed in Table 5. The data in Tables 5 and 8 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 8 for Magnitude of Interaction.***

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
Atazanavir/Ritonavir	↓ Atazanavir ↑ Nevirapine	Do not co-administer nevirapine with atazanavir because nevirapine substantially decrease atazanavir exposure
Clarithromycin	↓ Clarithromycin ↑ 14-OH Clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against <i>Mycobacterium avium-intracellulare complex</i> , overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.

<b>Drug Name</b>	<b>Effect on Concentration of Nevirapine or Concomitant Drug</b>	<b>Clinical Comment</b>
Efavirenz	↓ Efavirenz	There has been no determination of appropriate doses for the safe and effective use of this combination [ <i>see Warnings and Precautions (5.4)</i> ].
Ethinyl estradiol and Norethindrone	↓ Ethinyl estradiol  ↓ Norethindrone	Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.
Fluconazole	↑ Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine-associated adverse events.
Fosamprenavir	↓ Amprenavir  ↑ Nevirapine	Co-administration of nevirapine and fosamprenavir without ritonavir is not recommended.
Fosamprenavir/Ritonavir	↓ Amprenavir  ↑ Nevirapine	No dosing adjustments are required when nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir twice daily.
Indinavir	↓ Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/Ritonavir	↓ Lopinavir	A dose increase of lopinavir/ritonavir tablets to 500/125 mg twice-daily is recommended when used in combination with nevirapine.  A dose increase of lopinavir/ritonavir oral solution to 533/133 mg twice daily with food is recommended in combination with nevirapine.  In children 6 months to 12 years of age receiving lopinavir/ritonavir solution, consideration should be given to increasing the dose of lopinavir/ritonavir to 13/3.25 mg/kg for those 7 to <15 kg; 11/2.75 mg/kg for those 15 to 45 kg; up to a maximum dose of 533/133 mg twice daily .  Refer to the lopinavir/ritonavir package insert for complete pediatric dosing instructions when lopinavir/ritonavir tablets are used in combination with nevirapine.

<b>Drug Name</b>	<b>Effect on Concentration of Nevirapine or Concomitant Drug</b>	<b>Clinical Comment</b>
Methadone	↓ Methadone	Methadone levels were decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Nelfinavir	↓Nelfinavir M8 Metabolite ↓Nelfinavir C <sub>min</sub>	The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug.  Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine-containing regimen may use rifabutin instead.
Saquinavir/Ritonavir	The interaction between nevirapine and saquinavir/ritonavir has not been evaluated.	The appropriate doses of the combination of nevirapine and saquinavir/ritonavir with respect to safety/efficacy have not been established.

<b>Potential Drug Interactions:</b>		
<b>Drug Class</b>	<b>Examples of Drugs</b>	
Antiarrhythmics	Amiodarone, disopyramide, lidocaine	Plasma Concentrations May Be Decreased
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide	Plasma Concentrations May Be Decreased
Antifungals	Itraconazole	Plasma concentrations of some azole antifungals may be decreased. Nevirapine and itraconazole should not be administered concomitantly due to a potential decrease in itraconazole plasma concentrations
Calcium channel blockers	Diltiazem, nifedipine, verapamil	Plasma Concentrations May Be Decreased
Cancer chemotherapy	Cyclophosphamide	Plasma Concentrations May Be Decreased
Ergot alkaloids	Ergotamine	Plasma Concentrations May Be Decreased
Immunosuppressants	Cyclosporin, tacrolimus, sirolimus	Plasma Concentrations May Be Decreased
Motility agents	Cisapride	Plasma Concentrations May Be Decreased

Drug Class	Examples of Drugs	
Opiate agonists	Fentanyl	Plasma Concentrations May Be Decreased
Antithrombotics	Warfarin	Plasma Concentrations May Be Increased. Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy: *Teratogenic Effects:*

#### Lamivudine and Zidovudine

Pregnancy Category C.

Fetal Risk Summary: There are no adequate and well-controlled studies of lamivudine and zidovudine in pregnant women. Clinical trial data demonstrate that maternal zidovudine treatment during pregnancy reduces vertical transmission of HIV-1 infection to the fetus. Animal reproduction studies performed with lamivudine and zidovudine showed increased embryotoxicity fetal malformations (zidovudine), and increased embryoletality (lamivudine). Lamivudine, Nevirapine, and Zidovudine Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations: Treatment of HIV during pregnancy optimizes the health of both mother and fetus. Clinical trial data reviewed by FDA demonstrate that maternal zidovudine treatment significantly reduces vertical transmission of HIV-1 infection to the fetus [see *Clinical Studies (14.2)*]. Published data suggest that combination antiretroviral regimens may reduce the rate of vertical transmission even further.

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

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

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

Zidovudine: A randomized, double-blind, placebo-controlled trial was conducted in HIV-1-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV-1 transmission. Zidovudine treatment during pregnancy reduced the rate of maternal-fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to 7.8% for infants born to mothers treated with zidovudine. There were no differences in pregnancy-related adverse events between the treatment groups. Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. The observed abnormalities included problems in embryogenesis (prior to 14 weeks) or were

recognized on ultrasound before or immediately after initiation of study drug [see *Clinical Studies (14.2)*].

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

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

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

## **Nevirapine**

### *Teratogenic Effects*

No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. The maternal and developmental no-observable-effect level dosages produced systemic exposures approximately equivalent to or approximately 50% higher in rats and rabbits, respectively, than those seen at the recommended daily human dose (based on AUC). In rats, decreased fetal body weights were observed due to administration of a maternally toxic dose (exposures approximately 50% higher than that seen at the recommended human clinical dose).

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

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with CD4<sup>+</sup> cell counts greater than 250 cells/mm<sup>3</sup> should not initiate Lamivudine, Nevirapine, and Zidovudine Tablets unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women [see

*Boxed Warning*].

### **8.3 Nursing Mothers**

#### **Lamivudine, Nevirapine, and Zidovudine**

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

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

### **8.4 Pediatric Use**

#### **Lamivudine, Nevirapine, and Zidovudine**

Lamivudine, Nevirapine, and Zidovudine Tablets should not be administered to pediatric patients weighing less than 30 kg, because it is a fixed-dose combination that cannot be adjusted for this patient population.

### **8.5 Geriatric Use**

#### **Lamivudine, Nevirapine, and Zidovudine**

Clinical studies of lamivudine, zidovudine or nevirapine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Lamivudine, Nevirapine, and Zidovudine Tablets are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) because it is a fixed-dose combination that cannot be adjusted.

### **8.6 Renal Impairment**

#### **Lamivudine, Nevirapine, and Zidovudine**

Reduction of the dosages of lamivudine and zidovudine is recommended for patients with impaired renal function. Patients with creatinine clearance less than 50 mL/min should not receive Lamivudine, Nevirapine, and Zidovudine Tablets because it is a fixed-dose combination that cannot be adjusted.

### **8.7 Hepatic Impairment**

#### **Lamivudine, Nevirapine, and Zidovudine**

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 are 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

### Lamivudine, Nevirapine, and Zidovudine Tablet

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

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

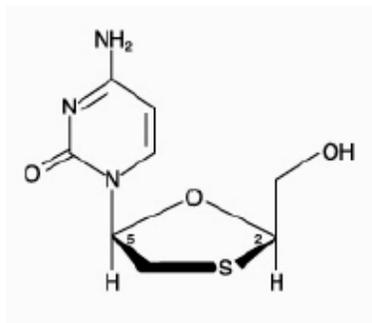
**Zidovudine:** Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, confusion, and 1 report of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

**Nevirapine:** There is no known antidote for nevirapine overdose. 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

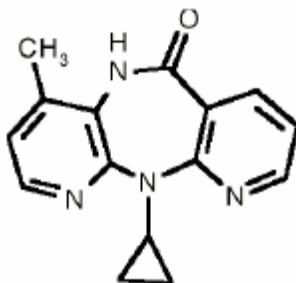
Lamivudine, Nevirapine, and Zidovudine Tablets are combination tablets containing lamivudine, nevirapine and zidovudine. Lamivudine and zidovudine (azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against HIV-1. Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Nevirapine is structurally a member of the dipyrindiazepinone chemical class of compounds.

Lamivudine: The chemical name of lamivudine is (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidine-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<sub>8</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S and a molecular weight of 229.26. It has the following structural formula:

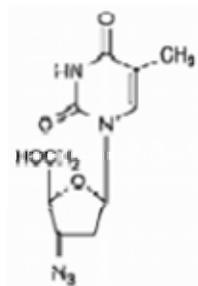


Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

Nevirapine: The chemical name of nevirapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido [3,2-b:2',3'-e][1,4] diazepin-6-one. Nevirapine is structurally a member of the dipyridodiazepinone chemical class of compounds. Nevirapine is a white to off-white crystalline powder with the molecular weight of 266.30 and the molecular formula C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O. Nevirapine has the following structural formula:



Zidovudine: The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub> and a molecular weight of 267.24. It has the following structural formula:



Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C.

Lamivudine, Nevirapine, and Zidovudine Tablets are for oral administration. Each film coated tablet contains 150mg Lamivudine, 200mg nevirapine, 300mg zidovudine and the inactive ingredients microcrystalline cellulose, lactose monohydrate, povidone K-25, colloidal silicon dioxide, sodium starch glycolate, magnesium stearate and Opadry White 13B58802. The film coating material Opadry White 13B58802 consists of hydroxypropyl methyl cellulose 2910, polyethylene glycol 400, polysorbate 80 and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY Lamivudine and Zidovudine

### 12.1 Mechanism of Action

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

### 12.3 Pharmacokinetics

**Lamivudine, Nevirapine, and Zidovudine Tablet:** One Lamivudine, Nevirapine, and Zidovudine Tablet was bioequivalent to one lamivudine (150 mg)/zidovudine (300 mg ) combination tablet (Combivir<sup>®</sup>) plus one nevirapine (200 mg) tablet (Viramune<sup>®</sup>) following single dose administration to fasting healthy adults (n = 35).

#### Lamivudine and Zidovudine

*Lamivudine:* The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 6. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

*Zidovudine:* The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 6. Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is GZDV. GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one-fifth of the zidovudine AUC.

**Table 6. Pharmacokinetic Parameters \* for Lamivudine and Zidovudine in Adults**

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

\*Data presented as mean ± standard deviation except where noted.

<sup>†</sup>Median [range].

<sup>‡</sup>Children.

<sup>§</sup> Adults.

<sup>||</sup> Approximate range.

Special Populations:

Pregnancy: See Use in Specific Populations (8.1).

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

Nursing Mothers: See Use in Specific Populations (8.3).

Pediatric Patients: Lamivudine, Nevirapine, and Zidovudine Tablets should not be administered to pediatric patients weighing less than 30 kg.

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

Gender: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in zidovudine AUC<sub>∞</sub> or lamivudine AUC<sub>∞</sub> normalized for body weight.

Race:

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

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

Drug Interactions: See Drug Interactions (7).

Table 7 presents drug interaction information for the individual components of lamivudine and zidovudine.

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

**Table 7. Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC\***

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

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

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

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

\*This table is not all inclusive.

†Estimated range of percent difference.

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

## Nevirapine

### Adults

#### 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  $93 \pm 9\%$  (mean  $\pm$  SD) for a 50 mg tablet and  $91 \pm 8\%$  for an oral solution. Peak plasma nevirapine concentrations of  $2 \pm 0.4$  mcg/mL ( $7.5 \mu\text{M}$ ) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady-state trough nevirapine concentrations of  $4.5 \pm 1.9$  mcg/mL ( $17 \pm 7 \mu\text{M}$ ), (n=242) were attained at 400 mg/day.

## Distribution

Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (V<sub>dss</sub>) of nevirapine was  $1.21 \pm 0.09$  L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is also found in breast milk [*see Use in Specific Populations* (8.3)]. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1 to 10 mcg/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% ( $\pm 5\%$ ) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

## Metabolism/Elimination

*In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the 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 <sup>14</sup>C-nevirapine, approximately  $91.4 \pm 10.5\%$  of the radiolabeled dose was recovered, with urine ( $81.3 \pm 11.1\%$ ) representing the primary route of excretion compared to feces ( $10.1 \pm 1.5\%$ ). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (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 to 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 to 400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma, from approximately 45 hours (single dose) to approximately 25 to 30 hours following multiple dosing with 200 to 400 mg/day.

## *Specific Populations*

### Renal Impairment

HIV-1 seronegative adults with mild (CrCL 50 to 79 mL/min; n=7), moderate (CrCL 30 to 49 mL/min; n=6), or severe (CrCL less than 30 mL/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 [*see Dosage and Administration (2.4) and Use in Specific Populations (8.6)*].

### Hepatic Impairment

In a steady-state trial comparing 46 subjects with mild (n=17; expansion of some portal areas; Ishak Score 1 to 2), moderate (n=20; expansion of most portal areas with occasional portal-to-portal and portal-to-central bridging; Ishak Score 3 to 4), or severe (n=9; marked bridging with occasional cirrhosis without decompensation indicating Child-Pugh A; Ishak Score 5 to 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/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.

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

### Gender

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.

### Race

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  $C_{\text{minss}}$  = 4.7 mcg/mL Black, 3.8 mcg/mL Hispanic, 4.3 mcg/mL Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

### Geriatric Patients

Nevirapine pharmacokinetics in HIV-1-infected adults do not appear to change with age (range 18 to 68 years); however, nevirapine has not been extensively evaluated in patients beyond the age

of 55 years [see Use in Specific Populations (8.5)].

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

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  $\mu\text{M}$ , a concentration that is unlikely to be achieved in patients as the therapeutic range is less than 25  $\mu\text{M}$ . 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 8 (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,  $C_{\text{max}}$ , and  $C_{\text{min}}$  of co-administered drugs are summarized.

**Table 8 Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Nevirapine (All interaction trials were conducted in HIV-1 positive subjects)**

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of Nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
				AUC	$C_{\text{max}}$	$C_{\text{min}}$
<b>Antiretrovirals</b>						
Atazanavir/Ritonavir <sup>a, d</sup>	300/100 mg QD day 4-13, then 400/100 mg QD day 14-23	200 mg BID day 1-23. Subjects were treated with nevirapine prior to trial entry	23	<u>Atazanavir 300/100 mg</u>	<u>Atazanavir 300/100 mg</u>	<u>Atazanavir 300/100 mg</u>
				↓42 (↓52 to ↓29)	↓28 (↓40 to ↓14)	↓72 (↓80 to ↓60)
				<u>Atazanavir 400/100 mg</u>	<u>Atazanavir 400/100 mg</u>	<u>Atazanavir 400/100 mg</u>
				↓19 (↓35 to ↑2)	↑2 (↓15 to ↑24)	↓59 (↓73 to ↓40)
Darunavir/Ritonavir <sup>e</sup>	400/100 mg BID	200 mg BID	8	↑24 (↓3 to ↑57)	↑40 (↑14 to ↑73)	↑2 (↓21 to ↑32)
Didanosine	100-150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	§
Efavirenz <sup>a</sup>	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)

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of Nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
				AUC	C <sub>max</sub>	C <sub>min</sub>
<b>Antiretrovirals</b>						
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 <sup>a</sup>	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 <sup>a,b</sup>	300/75 mg/m <sup>2</sup> (lopinavir/ritonavir) <sup>b</sup>	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15 <sup>c</sup>	↓22 (↓44 to ↑9)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓19)
Lopinavir <sup>a</sup>	400/100 mg BID (lopinavir/ritonavir)	200 mg QD x 14 days; 200 mg BID > 1 year	22, 19 <sup>c</sup>	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Maraviroc <sup>f</sup>	300 mg SD	200 mg BID	8	↑1 (↓35 to ↑55)	↑54 (↓6 to ↑151)	⇔
Nelfinavir <sup>a</sup>	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	⇔	⇔	↓32 (↓50 to ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)
Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	⇔	⇔	⇔
Stavudine	30-40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	⇔	⇔	§
Zalcitabine	0.125-0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	⇔	⇔	§
Zidovudine	100-200 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓28 (↓40 to ↓4)	↓30 (↓51 to ↑14)	§

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of Nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
Other Medications				AUC	C <sub>max</sub>	C <sub>min</sub>
Clarithromycin <sup>a</sup>	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 <sup>a</sup> and Norethindrone <sup>a</sup>	0.035 mg (as Ortho-Novum® 1/35) 1 mg (as Ortho-Novum® 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	↔	§
				↓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 <sup>a</sup>	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 <sup>a</sup>	Individual Subject Dosing	200 mg QD x 14 days; 200 mg BID ≥ 7 days	9	In a controlled pharmacokinetic trial with 9 subjects receiving chronic methadone to whom steady-state nevirapine therapy was added, the clearance of methadone was increased by 3-fold resulting in symptoms of withdrawal, requiring dose adjustments in 10 mg segments, in 7 of the 9 subjects. Methadone did not have any effect on nevirapine clearance.		
Rifabutin <sup>a</sup>	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 <sup>a</sup>	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑11 (↓4 to ↑28)	↔	§

§ = C<sub>min</sub> below detectable level of the assay

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

<sup>a</sup> For information regarding clinical recommendations see *Drug Interactions* (7).

<sup>b</sup> Pediatric subjects ranging in age from 6 months to 12 years

<sup>c</sup> Parallel group design; n for nevirapine +lopinavir/ritonavir, n for lopinavir/ritonavir alone

<sup>d</sup> 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.

<sup>e</sup> Based on between-trial comparison.

<sup>f</sup> 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 8 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

### Lamivudine and Zidovudine

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

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

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

*Lamivudine:* The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays.  $EC_{50}$  values (50% effective concentrations) were in the range of 0.003 to 15  $\mu$ M (1  $\mu$ M = 0.23 mcg/mL). HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median  $EC_{50}$  values of 0.429  $\mu$ M (range: 0.200 to 2.007  $\mu$ M) from Virco (n = 92 baseline samples from COL40263) and 2.35  $\mu$ M (1.37 to 3.68  $\mu$ M) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The  $EC_{50}$  values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120  $\mu$ M, and against HIV-2 isolates from 0.003 to 0.120  $\mu$ M in peripheral blood mononuclear cells. Ribavirin (50  $\mu$ M) 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  $\mu$ M (1  $\mu$ M = 0.27 mcg/mL) and 0.1 to 9  $\mu$ M, respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median  $EC_{50}$  values of 0.011  $\mu$ M (range: 0.005 to 0.110  $\mu$ M) from Virco (n = 92 baseline samples from COL40263) and 0.0017  $\mu$ M (0.006 to 0.0340  $\mu$ M) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The  $EC_{50}$  values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02  $\mu$ M,

and against HIV-2 isolates from 0.00049 to 0.004  $\mu$ M. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, and zalcitabine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

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

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

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

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

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

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

*Lamivudine:* See Lamivudine Plus Zidovudine (above).

*Zidovudine:* In a study of 167 HIV-1-infected patients, isolates ( $n = 2$ ) with multi-drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for  $\geq 1$  year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated amino acid substitutions with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M substitution being most commonly associated with multi-drug resistance. The substitution at codon 151 in combination with substitutions at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine,

zalcitabine, and zidovudine. Thymidine analogue mutations (TAMs) are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

## **Nevirapine**

### *Mechanism of Action*

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

### *Antiviral Activity*

The antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte-derived macrophages, and lymphoblastoid cell lines. In an assay using human embryonic kidney 293 cells, the median EC<sub>50</sub> value (50% inhibitory concentration) of nevirapine was 90 nM against a panel of 2923 isolates of HIV-1 that were primarily (93%) clade B clinical isolates from the United States. The 99<sup>th</sup> percentile EC<sub>50</sub> value was 470 nM in this trial. The median EC<sub>50</sub> value was 63 nM (range 14 to 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. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin in cell culture.

### *Resistance*

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 ZDV (n=14) were monitored in Phase 1 and 2 trials over 1 to  $\geq 12$  weeks. 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.

#### *Cross-resistance*

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

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Lamivudine and Zidovudine**

Carcinogenicity: Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection.

*Zidovudine:* Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

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

Mutagenicity: Lamivudine: Lamivudine was mutagenic in an L5178Y/TK<sup>+/-</sup> mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was negative in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

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

Impairment of Fertility: Lamivudine: In a study of reproductive performance, lamivudine,

administered to male and female rats at doses up to 130 times the usual adult dose based on body surface area considerations, revealed no evidence of impaired fertility (judged by conception rates) and no effect on the survival, growth, and development to weaning of the offspring.

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

### **Nevirapine**

Long-term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, 375 or 750 mg/kg/day for two years. Hepatocellular adenomas and carcinomas were increased at all doses in males and at the two high doses in females. In studies in which rats were administered nevirapine at doses of 0, 3.5, 17.5 or 35 mg/kg/day for two years, an increase in hepatocellular adenomas was seen in males at all doses and in females at the high dose. The systemic exposure (based on AUCs) at all doses in the two animal studies was lower than that measured in humans at the 200 mg twice daily dose. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included microbial assays for gene mutation (Ames: Salmonella strains and *E. coli*), mammalian cell gene mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is not known. In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of nevirapine.

## **13.2 Reproductive and Developmental Toxicology Studies**

### **Lamivudine and Zidovudine**

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

Zidovudine: Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one-sixth of dose) achieved with the recommended daily dose (100 mg every 4 hours). In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated AUC in rats at this dose level was 300 times the daily

AUC in humans given 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

### 13.3 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 Lamivudine and Zidovudine

### 14.1 Adults

#### Lamivudine and Zidovudine

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 study comparing continued current therapy (zidovudine alone [62% of patients] or zidovudine with didanosine or zalcitabine [38% of patients] to the addition of lamivudine tablet or lamivudine tablet 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/mm<sup>3</sup> 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 9.

**Table 9. Number of Patients (%) With At Least 1 HIV-1 Disease-Progression Event or Death**

Endpoint	Current Therapy (n=460)	Lamivudine Tablet plus Current Therapy (n = 896)	Lamivudine Tablet plus a NNRTI* 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 (3.0%)

\*An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

#### Nevirapine

Trial BI 1090 was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1 infected subjects with less than 200 CD4<sup>+</sup> cells/mm<sup>3</sup> 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<sup>+</sup> cell count of 96 cells/mm<sup>3</sup> and a baseline HIV-1 RNA of 4.58 log<sub>10</sub> copies/mL (38,291 copies/mL). Prior to entering the trial, 45% had previously experienced an AIDS-defining clinical event. Eighty-nine percent had antiretroviral treatment prior to entering the trial. BI 1090 was originally designed as a clinical endpoint 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 10.

**Table 10 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 <sup>1</sup> while <50 copies/mL	5	1
Discontinued trial therapy due to AE	7	6
Discontinued trial <48 weeks <sup>2</sup>	9	10

<sup>1</sup> including change to open-label nevirapine

<sup>2</sup> includes withdrawal of consent, lost to follow-up, non-compliance with protocol, other administrative reasons

At two years into the trial, 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<sup>+</sup> cell counts of 200 to 600 cells/mm<sup>3</sup> 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<sub>10</sub> copies/mL (25,704 copies/mL) and mean baseline CD4<sup>+</sup> cell count of 376 cells/mm<sup>3</sup>. The primary endpoint was the proportion of subjects with HIV-1 RNA less than 400 copies/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<sup>+</sup> cell counts in the nevirapine + ZDV + ddI group increased above baseline by a mean of 139 cells/mm<sup>3</sup> at one year, significantly greater than the increase of 87 cells/mm<sup>3</sup> in the ZDV + ddI subjects. The nevirapine + ZDV group mean decreased by 6 cells/mm<sup>3</sup> below baseline.

## 14.2 Prevention of Maternal-Fetal HIV-1 Transmission

The utility of zidovudine alone for the prevention of maternal-fetal HIV-1 transmission was demonstrated in a randomized, double-blind, placebo-controlled trial conducted in HIV-1-infected pregnant women with CD4<sup>+</sup> cell counts of 200 to 1,818 cells/mm<sup>3</sup> (median in the treated group: 560 cells/mm<sup>3</sup>) who had little or no previous exposure to zidovudine. Oral zidovudine was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by IV administration of zidovudine during labor and delivery. Following birth, neonates received oral zidovudine syrup for 6 weeks. The study showed a statistically significant difference in the incidence of HIV-1 infection in the neonates (based on viral culture from peripheral blood) between the group receiving zidovudine and the group receiving placebo. Of 363 neonates evaluated in the study, the estimated risk of HIV-1 infection was 7.8% in the group receiving zidovudine and 24.9% in the placebo group, a relative reduction in transmission risk of 68.7%. Zidovudine was well tolerated by mothers and infants. There was no difference in

pregnancy-related adverse events between the treatment groups.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Lamivudine, Nevirapine, and Zidovudine Tablets, containing 150 mg Lamivudine, 200 mg nevirapine, and 300 mg zidovudine, are white colored, oval shaped film coated biconvex tablets having 'ML' and '20' debossed on one side of the tablet and having plain surface on other side.

They are available as follows:

60 Tablets/Bottle (NDC 33342-073-09)

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

## 17 PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide

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

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

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

### 17.1 Advice for the Patient

Neutropenia and Anemia: Patients should be informed that the important toxicities associated with zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV-1 disease [see *Boxed Warning, Warnings and Precautions (5.1)*].

Myopathy: Patients should be informed that myopathy and myositis with pathological changes, similar to that produced by HIV-1 disease, have been associated with prolonged use of zidovudine [see *Boxed Warning, Warnings and Precautions (5.2)*].

Lactic Acidosis/Hepatomegaly: Patients should be informed that some HIV medicines, including Lamivudine, Nevirapine, and Zidovudine Tablets, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) [see *Boxed Warning, Warnings and Precautions (5.3)*].

HIV-1/HBV Co-infection: Patients co-infected with HIV-1 and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician [see *Warnings and Precautions (5.4)*].

Use With Other Lamivudine, Zidovudine, and/or Emtricitabine-Containing Products: Lamivudine, Nevirapine, and Zidovudine Tablets should not be coadministered with drugs containing lamivudine, zidovudine, or emtricitabine, including EPIVIR (lamivudine), EPIVIR-HBV (lamivudine), RETROVIR (zidovudine), EPZICOM (abacavir sulfate and lamivudine), TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine) ATRIPLA (efavirenz, emtricitabine, and tenofovir),

EMTRIVA (emtricitabine), TRUVADA (emtricitabine and tenofovir), or COMPLERA (rilpivirine/emtricitabine/tenofovir) [see *Warnings and Precautions* (5.5)].

HIV-1/HCV Co-Infection: Patients with HIV-1/HCV co-infection should be informed 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* (5.6)].

Hepatotoxicity and Skin Reactions: **Inform Patients of the possibility of severe liver disease or skin reactions associated with nevirapine, a component of Lamivudine, Nevirapine, and Zidovudine Tablets, 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 treatment. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of hepatic events and skin reactions. Advise patients with signs and symptoms of hepatitis to discontinue Lamivudine, Nevirapine, and Zidovudine Tablets and seek medical evaluation immediately. If Lamivudine, Nevirapine, and Zidovudine Tablets is discontinued due to hepatotoxicity, do not restart it. Patients, particularly women, with increased CD4<sup>+</sup> cell count at initiation of nevirapine therapy (greater than 250 cells/mm<sup>3</sup> in women and greater than 400 cells/mm<sup>3</sup> 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 are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT [see *Boxed Warning and 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 nevirapine 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 nevirapine-associated rash [see *Boxed Warning and Warnings and Precautions* (5.2)].

Drug Interactions: Patients should be cautioned about the use of other medications, including ganciclovir, interferon alfa, and ribavirin, which may exacerbate the toxicity of zidovudine. Also, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort [see *Drug Interactions*

(7.3)].

Contraceptives: Hormonal methods of birth control, other than depomedroxy-progesterone acetate (DMPA), should not be used as the sole method of contraception in women taking Lamivudine, Nevirapine, and Zidovudine Tablets, since nevirapine may lower the plasma levels of these medications. Additionally, when oral contraceptives are used for hormonal regulation during nevirapine therapy, the therapeutic effect of the hormonal therapy should be monitored [*see Drug Interactions (7)*].

Methadone: Nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Monitor methadone-maintained patients beginning nevirapine therapy for evidence of withdrawal and adjust methadone dose accordingly [*see Drug Interactions (7)*].

Redistribution/Accumulation of Body Fat: Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time [*see Warnings and Precautions (5.9)*].

Information About HIV-1 Infection: Lamivudine, Nevirapine, and Zidovudine Tablets are not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using Lamivudine, Nevirapine, and Zidovudine Tablets.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Lamivudine, nevirapine, and zidovudine are excreted in human breast milk. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Patients should be informed to take all HIV medications exactly as prescribed.

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Manufactured by:

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

## **MEDICATION GUIDE**

### **Lamivudine, Nevirapine, and Zidovudine Tablets, 150/200/300 mg**

#### **Rx Only**

**Generic name:** Lamivudine (lah MIH vue deen), nevirapine (na VAIR a peen), zidovudine (zye DOE vue deen) tablets

Read this Medication Guide before you start taking Lamivudine, Nevirapine, and Zidovudine Tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

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

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

**1. Severe liver problems:** Anyone who takes nevirapine, one of the components of Lamivudine, Nevirapine, and Zidovudine Tablets, may get severe liver problems. In some cases these liver problems can lead to liver failure and the need for a liver transplant, or death.

People who have a higher CD4<sup>+</sup> cell count when they begin lamivudine, nevirapine and zidovudine tablets treatment have a higher risk of liver problems, especially:

- Women with CD4<sup>+</sup> counts higher than 250 cells/mm<sup>3</sup>. This group has the highest risk.
- Men with CD4<sup>+</sup> counts higher than 400 cells/mm<sup>3</sup>.

If you are a woman with CD4<sup>+</sup> counts higher than 250 cells/mm<sup>3</sup> or a man with CD4<sup>+</sup> counts higher than 400 cells/mm<sup>3</sup>, you and your doctor will decide whether starting nevirapine is right for you.

In general, women have a higher risk of liver problems compared to men.

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

You may get a rash if you have liver problems.

**Stop taking lamivudine, nevirapine and zidovudine tablets and call your doctor right away if you have any of the following symptoms of liver problems:**

- dark (tea colored) urine
- yellowing of your skin or whites of your eyes

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

Your doctor should see you and do blood tests often to check your liver function during the first 18 weeks of treatment with nevirapine, one of the components of Lamivudine, Nevirapine, and Zidovudine Tablets. You should continue to have your liver checked regularly during your treatment with nevirapine. It is important for you to keep all of your doctor appointments.

**2. Severe rash and skin reactions:** Skin rash is the most common side effect of Nevirapine, one of the components of Lamivudine, Nevirapine, and Zidovudine Tablets. Most rashes happen in the first 6 weeks of taking lamivudine, nevirapine and zidovudine. **Rashes and skin reactions may be severe, life-threatening, and in some people, may lead to death. Stop using Lamivudine, Nevirapine, and Zidovudine Tablets and call your doctor right away if you get a rash with any of the following symptoms:**

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

**If your doctor tells you to stop treatment with Lamivudine, Nevirapine, and Zidovudine Tablets because you have had any of the serious liver or skin problems described above, you should never take nevirapine again.**

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

### **What is Lamivudine, Nevirapine, and Zidovudine Tablets?**

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

They are in a category of anti-HIV medicines called “nucleoside analogue reverse transcriptase inhibitors” and “non-nucleoside reverse transcriptase inhibitor” (NNRTI).

All three medicines work by lowering the amount of HIV in your blood (“viral load”). **You may take Lamivudine, Nevirapine, and Zidovudine Tablets with other anti-HIV medicines.** When you take Lamivudine, Nevirapine, and Zidovudine Tablets with other anti- HIV medicines, lamivudine, nevirapine and zidovudine can lower your viral load and increase the number of CD4<sup>+</sup> cells (“T cells”). CD4<sup>+</sup> cells are a type of immune helper cell in the blood. Lamivudine, Nevirapine, and Zidovudine Tablets may not have these effects in every person.

Lamivudine, Nevirapine, and Zidovudine tablets do not cure HIV or AIDS, and it is not known if

it will help you live longer with HIV. People taking Lamivudine, Nevirapine, and Zidovudine Tablets may still get infections common in people with HIV (opportunistic infections). It is very important that you stay under the care of your doctor.

It is not known if Lamivudine, Nevirapine, and Zidovudine Tablets lower the chance of passing HIV to other people. Effective treatment combined with safer sex practices, may reduce the chance of passing HIV to others through sexual contact. Always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Never reuse or share needles. Take your HIV medicines as prescribed.

### **Who should not take Lamivudine, Nevirapine, and Zidovudine Tablets?**

Tell your doctor if you have or have had liver problems. Your doctor may tell you not to take lamivudine, nevirapine and zidovudine if you have certain liver problems.

Lamivudine, Nevirapine, and Zidovudine Tablets are only for people diagnosed with HIV. If you have not been diagnosed as HIV positive, then do not take Lamivudine, Nevirapine, and Zidovudine Tablets.

### **What should I tell my doctor before taking Lamivudine, Nevirapine, and Zidovudine Tablets?**

#### **Before you take Lamivudine, Nevirapine, and Zidovudine Tablets, tell your doctor 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?**” and “**Who should not take Lamivudine, Nevirapine, and Zidovudine Tablets?**”
- receive dialysis
- have skin problems, such as a rash
- are pregnant or plan to become pregnant. It is not known if Lamivudine, Nevirapine, and Zidovudine Tablets will harm your unborn baby.
- are breast-feeding or plan to breast-feed. Lamivudine, nevirapine and zidovudine can pass into your breast milk and may harm your baby. It is also recommended that HIV-positive women should not breast-feed their babies. Do not breast-feed during treatment with lamivudine, nevirapine and zidovudine. Talk to your doctor about the best way to feed your baby.

**Tell your doctor and pharmacist about all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements.

Lamivudine, Nevirapine, and Zidovudine Tablets may affect the way other medicines work, and other medicines may affect how Lamivudine, Nevirapine, and Zidovudine Tablets works.

You should not take Lamivudine, Nevirapine, and Zidovudine Tablets if you also take:

- St. John’s Wort. St. John’s Wort can lower the amount of nevirapine in your body.
- efavirenz (Sustiva<sup>®</sup>, Atripla<sup>®</sup>). Efavirenz may cause you to have an increased chance of side effects.
- atazanavir (Reyataz<sup>®</sup>)

- lopinavir and ritonavir (Kaletra<sup>®</sup>)
- fosamprenavir calcium (Lexiva<sup>®</sup>)
- itraconazole (Sporanox<sup>®</sup>)
- ketoconazole (Nizoral<sup>®</sup>)
- rifampin (Rifadin<sup>®</sup>, Rifamate<sup>®</sup>, Rifater<sup>®</sup>)
- Birth control pills. Birth control pills taken by mouth (oral contraceptives) and other hormone types of birth control may not work to prevent pregnancy. Talk with your doctor about other types of birth control that you can use to prevent pregnancy during treatment with lamivudine, nevirapine and zidovudine tablets.

Also tell your doctor if you take:

- clarithromycin (Biaxin<sup>®</sup>)
- fluconazole (Diflucan<sup>®</sup>)
- indinavir sulfate (Crixivan<sup>®</sup>)
- methadone
- nelfinavir mesylate (Viracept<sup>®</sup>)
- rifabutin (Mycobutin<sup>®</sup>)
- warfarin (Coumadin<sup>®</sup>, Jantoven<sup>®</sup>)
- saquinavir mesylate (Invirase<sup>®</sup>)

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

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

### **How should I take Lamivudine, Nevirapine, and Zidovudine Tablets?**

- Lamivudine, Nevirapine, and Zidovudine Tablets may be taken in combination with other anti-HIV medications.
- Take Lamivudine, Nevirapine, and Zidovudine Tablets exactly as your doctor tells you to take it. Do not change your dose unless your doctor tells you to.
- You should never take more than one form of Lamivudine, Nevirapine, and Zidovudine Tablets at the same time. Talk to your doctor if you have any questions
- Take Lamivudine, Nevirapine, and Zidovudine Tablets without food.
- Do not miss a dose of Lamivudine, Nevirapine, and Zidovudine Tablets, because this could make HIV harder to treat. 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, just take the next dose at your regular time. Do not take two doses at the same time.

### **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?**"
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV 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 doctor if you start having new symptoms after starting your HIV medicine.
- **Changes in body fat** can happen in some people who take antiretroviral therapy. These changes

may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the middle of your body (trunk). Loss of fat from your legs, arms, and face can also happen. The cause and long-term health effects of these problems are not known at this time.

The most common side effect of Lamivudine, Nevirapine, and Zidovudine Tablets is rash.

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Lamivudine, Nevirapine, and Zidovudine Tablets. For more information, ask your doctor 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 at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]
- Throw away Lamivudine, Nevirapine, and Zidovudine Tablets that are no longer needed or out-of-date.

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

### **General information about 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.

This Medication Guide summarizes the most important information about Lamivudine, Nevirapine, and Zidovudine Tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Lamivudine, Nevirapine, and Zidovudine Tablets that is written for health professionals.

For more information, call Macleods Pharmaceuticals Ltd. at 314-814-2833.

### **What are the ingredients in Lamivudine, Nevirapine, and Zidovudine Tablets?**

Active Ingredients: lamivudine USP, nevirapine USP and zidovudine USP

Inactive ingredients: colloidal silicon dioxide, corn starch, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. The tablets are coated with opadry white contains hypromellose, polyethylene glycol, polysorbate 80 and titanium dioxide.

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

Manufactured by:

Macleods Pharmaceuticals Ltd.

Baddi, Himachal Pradesh, INDIA

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