

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lamivudine, Zidovudine and Nevirapine tablets 150/300/200mg safely and effectively. See full prescribing information for Lamivudine, Zidovudine and Nevirapine tablets 150/300/200mg.

Lamivudine, Zidovudine and Nevirapine tablets 150/300/200mg

WARNING: RISK OF HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B, 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 and Nevirapine tablets. (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 and Nevirapine tablets. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.4)
- Fatal and non-fatal hepatotoxicity (5.8)
- Fatal and non-fatal skin reactions (5.9)

Discontinue immediately if experiencing:

- Signs or symptoms of hepatitis (5.8)
- Increased transaminases combined with rash or other systemic symptoms (5.8)
- Severe skin or hypersensitivity reactions (5.9)
- Any rash with systemic symptoms (5.9)

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, Zidovudine and Nevirapine tablets, a combination of two nucleoside analogue reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor, is indicated 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, 5.8)
 - adult females with CD4⁺ cell counts greater than 250 cells/mm³
 - adult males with CD4⁺ cell counts greater than 400 cells/mm³
- The 14-day lead-in period must be strictly followed; it has been demonstrated to reduce the frequency of rash (2, 5.9)

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

Adult

Lead-in Period (Initial 14 days of dosing): One Lamivudine, Zidovudine and Nevirapine Tablet, 150 mg/300 mg/200 mg taken once per day followed by a daily oral dose of lamivudine 150 mg and zidovudine 300 mg 12 hours later.

Maintenance: One Lamivudine, Zidovudine and Nevirapine Tablet, 150 mg/300 mg/200 mg taken twice daily.

Pediatrics

Lamivudine, Zidovudine and Nevirapine Tablets are a fixed dose combination of lamivudine, zidovudine and nevirapine. It is recommended for pediatric patients ≥ 12 years of age and weighing ≥ 50 kgs.

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

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

-----CONTRAINDICATIONS-----

Lamivudine, Zidovudine and Nevirapine tablets are contraindicated in

- Patients who are just initiating therapy with nevirapine. (4)
- Patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis, Stevens-Johnson syndrome). (4.1)

- Patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment. (4.2, 5.8, 8.7)
- Use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens, an unapproved use. (4.3, 5.8)

-----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)
- Lamivudine, Zidovudine and Nevirapine 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, Zidovudine and Nevirapine 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 co-infected 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)
- Hepatotoxicity: Fatal and non-fatal hepatotoxicity has been reported. Monitor liver function tests before and during therapy. Permanently discontinue nevirapine if clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur. Do not restart nevirapine after recovery. (5.8)
- 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. (5.9)
- Immune reconstitution syndrome (5.12) and redistribution/accumulation of body fat (5.13) have been reported in patients treated with combination antiretroviral therapy.

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

- Most commonly reported adverse reactions (incidence greater than or equal to 15%) in adult and pediatric HIV-1 clinical studies of combination lamivudine and zidovudine were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. (6.1)
- The most common adverse reaction with nevirapine is rash. In adults the incidence of rash is 15% vs 6% with placebo, with Grade 3/4 rash occurring in 2% of subjects. (6.1)
- In pediatric subjects the incidence of rash (all causality) was 21%. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 1-866-604-3268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Concomitant use with the following drugs should be avoided: stavudine (7.1), zalcitabine (7.1), doxorubicin (7.2).
- Bone marrow suppressive/cytotoxic agents: May increase the hematologic toxicity of zidovudine. (7.3)
- Co-administration of Lamivudine, Zidovudine and Nevirapine tablets 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 (5.11, 7.6, 12.3)

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

- Nursing Mothers: HIV-1 infected mothers 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 nevirapine to patients with Child-Pugh B or C (5.8, 8.7)
- No dose adjustment is required for patients with renal impairment.
- Patients on dialysis receive an additional dose of 200 mg following each dialysis treatment (8.6)

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, LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY AND SKIN REACTIONS

Lamivudine, Zidovudine and Nevirapine tablets is not intended for use in patients who are just initiating therapy with nevirapine. Lamivudine, Zidovudine and Nevirapine tablets should be administered only to patients who have received zidovudine + lamivudine (standard doses) + nevirapine (200 mg o.d) for 2 weeks and have demonstrated adequate tolerability to nevirapine [*see Indications (1)*].

Hematologic Toxicity: Zidovudine, one of the active ingredients in Lamivudine, Zidovudine and Nevirapine 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, Zidovudine and Nevirapine tablets. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Lamivudine, Zidovudine and Nevirapine 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. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher CD4⁺ cell counts at initiation of therapy place patients at increased risk; women with CD4⁺ cell counts greater than 250 cells/mm³, including pregnant women receiving nevirapine in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk. However, hepatotoxicity associated with nevirapine use can occur in both genders, all CD4⁺ cell counts and at any time during treatment. Hepatic failure has also been

reported in patients without HIV taking nevirapine for post-exposure prophylaxis (PEP). Use of nevirapine for occupational and non-occupational PEP is contraindicated [see *Contraindications (4.3)*]. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue Lamivudine, Zidovudine and Nevirapine tablets and seek medical evaluation immediately [see *Warnings and Precautions (5.8)*].

Skin Reactions: Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue Lamivudine, Zidovudine and Nevirapine tablets and seek medical evaluation immediately. Transaminase levels should be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. The 14-day lead-in period with nevirapine 200 mg daily dosing has been observed to decrease the incidence of rash and must be followed [see *Warnings and Precautions (5.9)*].

Monitoring: Patients must be monitored intensively during the first 18 weeks of therapy with Lamivudine, Zidovudine and Nevirapine tablets to detect potentially life-threatening hepatotoxicity or skin reactions. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart Lamivudine, Zidovudine and Nevirapine tablets following clinical hepatitis, or transaminase elevations combined with rash or other systemic symptoms, or following severe skin rash or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment. In addition, the 14-day lead-in period with nevirapine 200 mg daily dosing must be strictly followed.

1 INDICATIONS AND USAGE

Lamivudine, Zidovudine and Nevirapine Tablets are indicated for the treatment of HIV-1 infection, once patients have demonstrated adequate tolerability to an initial two weeks of treatment with nevirapine 200 mg taken once daily in combination with lamivudine and zidovudine twice daily.

The following points should be considered when initiating therapy with Lamivudine, Zidovudine and Nevirapine Tablets:

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled trials, nevirapine should not be initiated in adult females with CD4⁺ cell counts greater than 250 cells/mm³ or in adult males with CD4⁺ cell counts greater than 400 cells/mm³ unless the benefit outweighs the risk [see *Boxed Warning and Warnings and Precautions (5.8)*].
- The 14-day lead-in period with nevirapine 200 mg once daily dosing has been demonstrated to reduce the frequency of rash [see *Dosage and Administration (2) and Warnings and Precautions (5.9)*].

2 DOSAGE AND ADMINISTRATION

2.1 Adults

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

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

One Lamivudine, Zidovudine and Nevirapine Tablet, 150 mg/300 mg/200 mg taken once per day followed by a daily oral dose of lamivudine 150 mg and zidovudine 300 mg 12 hours later.

Maintenance:

If the initial 14 days of nevirapine is tolerated without any hypersensitivity reactions [e.g. rash, liver function test abnormalities; *see Warnings and Precautions (5.8, 5.9)*], the recommended maintenance oral dose is one Lamivudine, Zidovudine and Nevirapine Tablet, 150 mg/300 mg/200 mg taken twice daily.

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

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

2.2 Pediatrics

Lamivudine, Zidovudine and Nevirapine Tablets are a fixed dose combination of lamivudine, zidovudine and nevirapine. It is recommended for pediatric patients ≥ 12 years of age and weighing ≥ 50 kgs.

2.3 Geriatrics

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

2.4 Renal Impairment

In view of the strengths of the individual drug components of this product, Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are not suitable for use in patients with renal impairment (creatinine clearance < 50 ml/min) or for patients on haemodialysis.

2.5 Hepatic Impairment

Lamivudine, Nevirapine and Zidovudine Fixed Dose Tablets are not suitable for patients with hepatic impairment.

2.6 Monitoring of patients

Zidovudine: Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve,

particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia [see *Warnings and Precautions (5.1)*]. In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant neutropenia (granulocyte count of <750 cells/mm³ or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed [see *Warnings and Precautions (5.1)*]. In patients who develop significant anemia, dose interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level and patient tolerance. For patients experiencing pronounced anemia while receiving chronic co-administration of Lamivudine, Zidovudine and Nevirapine Tablets and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 7, discontinuation of Lamivudine, Zidovudine and Nevirapine Tablets may be considered.

Nevirapine: Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment with nevirapine. The optimal frequency of monitoring during this period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation, and at two weeks post dose escalation. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment [see *Warnings and Precautions (5.8)*]. In some cases, hepatic injury has progressed despite discontinuation of treatment.

Lamivudine, Zidovudine and Nevirapine Tablets should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings. Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their nevirapine dose increased until the rash has resolved [see *Warnings and Precautions (5.9)*]. Lamivudine, Zidovudine and Nevirapine Tablets can cause hepatitis. If clinical hepatitis occurs, Lamivudine, Zidovudine and Nevirapine Tablets should be discontinued. Do not restart Lamivudine, Zidovudine and Nevirapine Tablets after recovery [see *Warnings and Precautions (5.8)*].

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

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

Note: Stavudine in combination with Lamivudine, Zidovudine and Nevirapine Fixed Dose Tablets is not recommended [*see Drug Interactions (7.1)*].

3 DOSAGE FORMS AND STRENGTHS

Lamivudine, Zidovudine and Nevirapine Tablets 150/300/200 mg, White capsule shaped, biconvex film-coated tablets, debossed with 'LZN' on one side and plain on other side.

4 CONTRAINDICATIONS

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

Lamivudine, Zidovudine and Nevirapine Tablets are contraindicated for patients who are just initiating therapy with nevirapine. These patients require a lead-in dose of nevirapine 200 mg q.d, whereas this formulation contains the maintenance dose of nevirapine 200 mg b.i.d [*see Indication and Usage (1)*].

4.1 Hypersensitivity

Lamivudine, Zidovudine and Nevirapine tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis, Stevens-Johnson syndrome) to any of the components of the product.

4.2 Hepatic Impairment

Lamivudine, Zidovudine and Nevirapine tablets is contraindicated in patients with moderate or severe (Child Pugh Class B or C, respectively) hepatic impairment [*see Warnings and Precautions (5.8) and Use in Specific Populations (8.7)*].

4.3 Post-Exposure Prophylaxis

Lamivudine, Zidovudine and Nevirapine tablets are contraindicated for use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens [*see Warnings and Precautions (5.8)*].

5 WARNINGS AND PRECAUTIONS

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

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

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

5.1 Hematologic Toxicity/Bone Marrow Suppression

Zidovudine, a component of Lamivudine, Zidovudine and Nevirapine tablets has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease. Lamivudine, Zidovudine and Nevirapine tablets should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count less than 1,000 cells/mm³ 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, Zidovudine and Nevirapine 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 Lamivudine, Zidovudine and Nevirapine 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, Zidovudine and Nevirapine 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, Zidovudine and Nevirapine 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 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 of hepatitis B viral DNA (HBV DNA). Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory 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, Zidovudine and Nevirapine Tablets contain a higher dose of the same active ingredient (lamivudine) than in EPIVIR-HBV[®] (lamivudine) tablets and oral Solution. EPIVIR-HBV was developed for treating chronic hepatitis B. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

Emergence of Lamivudine-Resistant HBV: In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see full prescribing information for EPIVIR-HBV 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, Zidovudine and Nevirapine tablets is a fixed-dose combination of lamivudine, zidovudine and nevirapine. Lamivudine, Zidovudine and Nevirapine tablets should not be administered concomitantly with other lamivudine- or zidovudine-containing products including EPIVIR[®] (lamivudine) Tablets and Oral Solution, EPIVIR-HBV Tablets and Oral Solution, RETROVIR[®] (zidovudine) Tablets, Capsules, Syrup, and IV Infusion, EPZICOM[®] (abacavir sulfate and lamivudine) Tablets, or TRIZIVIR[®] (abacavir sulfate, lamivudine, and zidovudine) Tablets; or emtricitabine-containing products, including ATRIPLA[®] (efavirenz, emtricitabine, and tenofovir), EMTRIVA[®] (emtricitabine), or TRUVADA[®] (emtricitabine and tenofovir) or COMPLERA[™] (rilpivirine/emtricitabine/tenofovir).

5.6 Use with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown that ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered 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, Zidovudine and Nevirapine tablets should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of Lamivudine, Zidovudine and Nevirapine 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 (eg, 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, Zidovudine and Nevirapine 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, Zidovudine and Nevirapine tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur [*see Adverse Reactions (6.1)*].

5.8 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. In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of subjects who received nevirapine and 1% of subjects in control groups.

The risk of symptomatic hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the nevirapine groups compared to controls through 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In some cases, subjects presented with nonspecific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately half of the subjects with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use. Patients with signs or symptoms of hepatitis must be advised to discontinue Lamivudine, Zidovudine and Nevirapine 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), and Patient Counseling Information (17.7)].

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

The patients at greatest risk of hepatic events, including potentially fatal events, are women with high CD4⁺ cell counts. In general, during the first 6 weeks of treatment, women have a 3-fold higher risk than men for symptomatic, often rash-associated, hepatic events (6% versus 2%), and patients with higher CD4⁺ cell counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4⁺ cell counts greater than 250 cells/mm³ had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with CD4⁺ cell counts less than 250 cells/mm³ (11% versus 1%). An increased risk was observed in men with CD4⁺ counts greater than 400 cells/mm³ (6% versus 1% for men with CD4⁺ cell counts less than 400 cells/mm³). However, all patients, regardless of gender, CD4⁺ cell counts, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4⁺ cell counts. Co-infection with hepatitis B or C and/or increased transaminase elevations at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-1 uninfected individuals receiving multiple doses of nevirapine in the setting of post-exposure prophylaxis (PEP), an unapproved use. Use of nevirapine for occupational and non-occupational PEP is contraindicated [see *Contraindications (4.3)*].

Increased nevirapine trough concentrations have been observed in some patients with hepatic fibrosis or cirrhosis. Therefore, carefully monitor patients with either hepatic fibrosis or cirrhosis for evidence of drug-induced toxicity. Do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [see *Contraindications (4.2)*, *Use in Specific Populations (8.7)*, and *Clinical Pharmacology (12.3)*].

5.9 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 1% of placebo subjects.

Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue Lamivudine, Zidovudine and Nevirapine tablets and seek medical evaluation immediately [*see Boxed Warning and Patient Counseling Information (17.7)*]. Do not restart Lamivudine, Zidovudine and Nevirapine tablets following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

If patients present with a suspected nevirapine-associated rash, transaminases should be measured immediately. Permanently discontinue Lamivudine, Zidovudine and Nevirapine tablets in patients with rash-associated transaminase elevations [*see Warnings and Precautions (5.8)*].

Therapy with Lamivudine, Zidovudine and Nevirapine tablets must be initiated with a 14-day lead-in period of 200 mg/day (150 mg/m²/day in pediatric patients), which has been shown to reduce the frequency of rash. Discontinue Lamivudine, Zidovudine and Nevirapine 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 (150 mg/m²/day in pediatric patients) until the rash has resolved. The total duration of the once-daily lead-in-dosing period should not exceed 28 days at which point an alternative regimen should be sought [*see Dosage and Administration (2)*]. Patients should be monitored closely if isolated rash of any severity occurs. Delay in stopping Lamivudine, Zidovudine and Nevirapine 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.

5.10 Resistance

Nevirapine must not be used as a single agent to treat HIV-1 or added on as a sole agent to a failing regimen. Resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential for cross resistance. When

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

5.11 Drug Interactions

See Table 5 for listings of established and potential drug interactions [see *Drug Interactions* (7.6)].

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

5.12 Immune Reconstitution Syndrome

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

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

5.13 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

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 in Adults

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

Lamivudine/Zidovudine

Lamivudine Plus Zidovudine Administered As Separate Formulations: In 4 randomized, controlled trials of EPIVIR 300 mg per day plus RETROVIR 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 EPIVIR 300 mg/day and RETROVIR 600 mg/day

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

Cough	18%
Skin	
Skin rashes	9%
Musculoskeletal	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received EPIVIR 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 EPIVIR 300 mg/day plus RETROVIR 600 mg/day^a

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

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

n = Number of patients assessed.

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

Nevirapine

The most serious adverse reactions associated with nevirapine are hepatitis, hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction [see *Boxed Warning and Warnings and Precautions (5.8, 5.9)*].

Hepatic Reaction

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of subjects who received nevirapine and 1% of subjects in control groups. Female gender and higher CD4⁺ cell counts (greater than 250 cells/mm³ in women and greater than 400 cells/mm³ in men) place patients at increased risk of these events [see *Boxed Warning and Warnings and Precautions (5.8)*].

Asymptomatic transaminase elevations (AST or ALT greater than 5 X 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 clinically toxicity of nevirapine is rash, which can be severe or life threatening [see *Boxed Warning and Warnings and Precautions (5.9)*]. 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 the development of nevirapine-associated rash [see *Boxed Warning and Warnings and Precautions (5.9)*].

Treatment-related, adverse experiences of moderate or severe intensity observed in greater than 2% of subjects receiving nevirapine in placebo-controlled trials are shown in Table 3.

Table 3. Percentage of Subjects with Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials

	Trial 1090 ¹		Trials 1037, 1038, 1046 ²	
	VIRAMUNE (n=1121)	Placebo (n=1128)	VIRAMUNE (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	9	4
Granulocytopenia	2	3	<1	0
Headache	1	<1	4	1
Fatigue	<1	<1	5	4
Diarrhea	<1	1	2	1
Abdominal pain	<1	<1	2	0
Myalgia	<1	0	1	2

¹ Background therapy included 3TC for all subjects and combinations of NRTIs and Pls. Subjects had CD4⁺ cell counts less than 200 cells/mm³.

² Background therapy included ZDV and ZDV + ddI; nevirapine monotherapy was administered in some subjects. Subjects had CD4⁺ cell count greater than or equal to 200 cells/mm³.

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

¹ Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had CD4⁺ cell counts less than 200 cells/mm³.

² Background therapy included ZDV and ZDV+ddI; nevirapine monotherapy was administered in some subjects. Subjects had CD4⁺ cell count greater than or equal to 200 cells/mm³.

6.2 Clinical Trials in Pediatric Subjects
Nevirapine

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

The safety of nevirapine was also examined in BI Trial 1100.1368, an open-label, randomized clinical trial performed in South Africa in which 123 HIV-1 infected treatment-naïve subjects between 3 months and 16 years of age received combination treatment with nevirapine oral suspension, lamivudine and zidovudine for 48 weeks [see *Use In Specific Populations (8.4) and Clinical Pharmacology (12.3)*]. Rash (all causality) was reported in 21% of the subjects, 4 (3%) of whom discontinued drug due to rash. All 4 subjects experienced the rash early in the course of therapy (less than 4 weeks) and resolved upon nevirapine discontinuation. Other clinically important adverse events (all causality) include neutropenia (9%), anemia (7%), and hepatotoxicity (2%) [see *Use in Specific Populations (8.4) and Clinical Studies (14.2)*].

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

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post-approval use of lamivudine, zidovudine and nevirapine. 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, zidovudine and nevirapine.

Lamivudine and Zidovudine

Body as a Whole: Redistribution/accumulation of body fat [see *Warnings and Precautions (5.13)*].

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, Steven-Johnson syndrome.

Nevirapine

Body as a Whole: fever, somnolence, drug withdrawal [see *Drug Interactions (7.6)*], redistribution/accumulation of body fat [see *Warnings and Precautions, (5.13)*].

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

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

7 DRUG INTERACTIONS

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

7.1 Antiretroviral Agents

Lamivudine: Zalcitabine: Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of Lamivudine, Zidovudine and Nevirapine tablets in combination with zalcitabine is not recommended.

Zidovudine: Stavudine: Concomitant use of Lamivudine, Zidovudine and Nevirapine 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 Doxorubicin

Zidovudine: Concomitant use of lamivudine/zidovudine with doxorubicin should be avoided since an antagonistic relationship with zidovudine has been demonstrated in vitro.

7.3 Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

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

7.4 Interferon- and Ribavirin-Based Regimens

Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co-administered 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* (5.6), *Clinical Pharmacology* (12.3)].

7.5 Trimethoprim/Sulfamethoxazole (TMP/SMX)

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

7.6 Nevirapine

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

The specific pharmacokinetic changes that occur with co-administration of nevirapine and other drugs are listed in *Clinical Pharmacology*, Table 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 decreases atazanavir exposure.

Clarithromycin	↓ Clarithromycin ↑ 14-OH clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against <i>Mycobacterium avium-intracellulare complex</i> , overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Efavirenz	↓ Efavirenz	There has been no determination of appropriate doses for the safe and effective use of this combination [see Warnings and Precautions (5.11)].
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; and up to a maximum dose of 533/133 mg twice daily. Refer to the lopinavir/ritonavir package insert for complete pediatric dosing instructions when lopinavir/ritonavir tablets are used in combination with nevirapine.
Methadone	↓ Methadone	Methadone levels were decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and the methadone dose should be adjusted accordingly.
Nelfinavir	↓ Nelfinavir M8 Metabolite ↓ Nelfinavir C _{min}	The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑ Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine-containing regimen may use rifabutin instead.
Saquinavir/Ritonavir	The interaction between nevirapine and saquinavir/ritonavir has not been evaluated	The appropriate doses of the combination of nevirapine and saquinavir/ritonavir with respect to safety and efficacy have not been established.

Potential Drug Interactions:

Drug class	Examples of Drugs	
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, sirolimus, tacrolimus	Plasma concentrations may be decreased.
Motility agents	Cisapride	Plasma concentrations may be decreased.
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

There are no adequate and well-controlled studies of lamivudine, zidovudine and nevirapine in pregnant women. Lamivudine, Zidovudine and Nevirapine Tablet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lamivudine and Zidovudine

Pregnancy Category C.

Fetal Risk Summary: Clinical trial data demonstrate that maternal zidovudine treatment during pregnancy reduces vertical transmission of HIV-1 infection to the fetus. Animal reproduction studies performed with lamivudine and zidovudine showed increased embryotoxicity and fetal malformations (zidovudine), and increased embryoletality (lamivudine).

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 embryolethality occurred in rabbits at exposure levels similar to those in humans. However, there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Based on animal studies, lamivudine crosses the placenta and is transferred to the fetus [*see Nonclinical Toxicology (13.2)*].

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

Nevirapine

Teratogenic Effects, Pregnancy Category B.

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).

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⁺ cell counts greater than 250 cells/mm³ should not initiate nevirapine unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women [*see Boxed Warning*].

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 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, Zidovudine and Nevirapine tablets.

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

8.4 Pediatric Use

The safety, pharmacokinetic profile, and virologic and immunologic responses of nevirapine have been evaluated in HIV-infected pediatric patients age 3 months to 18 years [*see Adverse Reactions (6.2) and Clinical Studies (14.2)*]. The safety and pharmacokinetic profile of nevirapine has been evaluated in HIV-infected pediatric patients age 15 days to less than 3 months [*see Adverse Reactions (6.2) and Clinical Studies (14.2)*].

The most frequently reported adverse events related to nevirapine in pediatric subjects were similar to those observed in adults, with the exception of granulocytopenia, which

was more commonly observed in children receiving both zidovudine and Nevirapine [*see Adverse Reactions (6.2) and Clinical Studies (14.2)*].

Lamivudine, Zidovudine and Nevirapine Tablets 150/300/200 mg should not be administered to pediatric patients less than 12 years of age or weighing less than 50 kg because it is a fixed-dose combination that cannot be adjusted for this patient population.

8.5 Geriatric Use

Clinical studies of lamivudine, zidovudine and 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. Because Lamivudine, Zidovudine and Nevirapine Tablets are a fixed-dose combination, they should not be prescribed for patients who require dose reduction or have renal impairment with CrCL <50 mL/min

8.6 Renal Impairment

Lamivudine/Zidovudine

Reduction of the dosages of lamivudine and zidovudine is recommended for patients with impaired renal function.

Nevirapine

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known. No adjustment in nevirapine dosing is required in patients with CrCL greater than or equal to 20 mL/min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated [*see Dosage and Administration (2) and Clinical Pharmacology (12.3)*].

Since Lamivudine, Zidovudine and Nevirapine tablet is a fixed-dose combination the dose cannot be adjusted. Hence, patients with creatinine clearance less than 50 mL/min should not receive Lamivudine, Zidovudine and Nevirapine tablet.

8.7 Hepatic Impairment

Lamivudine/Zidovudine

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis.

Nevirapine

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [*see*

Contraindications (4.2), Warnings and Precautions (5.8), and Clinical Pharmacology (12.3)].

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

10 OVERDOSAGE

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

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

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.

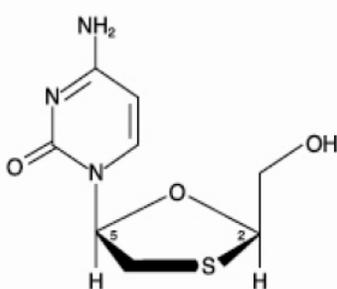
Nevirapine: There is no known antidote for nevirapine overdose. Cases of nevirapine overdose at doses ranging from 800 to 1800 mg per day for up to 15 days have been reported. Patients have experienced events including edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates,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

11 DESCRIPTION

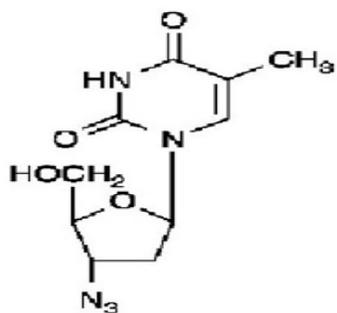
Lamivudine, Zidovudine and Nevirapine Tablets contain a fixed dose combination of lamivudine, zidovudine and nevirapine. Lamivudine and zidovudine are synthetic nucleoside analogues with activity against human immunodeficiency virus (HIV-1). Both drugs act by terminating the growth of the DNA chain and inhibiting the reverse transcriptase of HIV-1. Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) specific for HIV-1 reverse transcriptase.

Lamivudine, Zidovudine and Nevirapine Tablets are for oral administration. Each tablet contains lamivudine 150 mg, zidovudine 300 mg and nevirapine 200 mg. The inactive ingredients in the tablets are microcrystalline cellulose, corn starch, povidone, sodium starch glycolate, magnesium stearate and a film coat containing hypromellose, titanium dioxide, and PEG 6000.

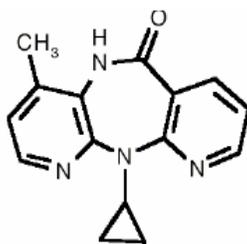
Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$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



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



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



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lamivudine, Zidovudine and Nevirapine tablets 150/300/200mg is an antiviral drug [*see Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

Pharmacokinetics in Adults

The rate and extent of absorption of lamivudine, zidovudine, and nevirapine from the combination tablets was similar to that from Combivir[®] tablets (150 mg lamivudine and 300 mg zidovudine) and Viramune[®] tablets (200 mg nevirapine), respectively, when administered to healthy volunteers in the fasted state.

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 3'-azido-3'-deoxy-5'-O-(beta)-D-glucopyranuronosylthymidine (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^a for Lamivudine and Zidovudine in Adults

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

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

^b Median [range].

^c Children.

^d Adults.

^c Approximate range.

Nevirapine

Absorption and Bioavailability

Nevirapine is readily absorbed (greater than 90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was $93 \pm 9\%$ (mean \pm SD) for a 50 mg tablet and $91 \pm 8\%$ for an oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 mcg/mL (7.5 micromolar) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady-state trough nevirapine concentrations of 4.5 ± 1.9 mcg/mL (17 ± 7 micromolar), (n=242) were attained at 400 mg/day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high-fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox[®] 30 mL), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate trial in HIV-1 infected subjects (n=6), nevirapine steady-state systemic exposure (AUC_t) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without antacid or didanosine.

Distribution

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

Metabolism/Elimination

In vivo trials in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion trial in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of ¹⁴C-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 20-25%, as indicated by erythromycin breath test results and urine metabolites. Autoinduction of CYP3A and CYP2B6 mediated metabolism leads to an approximately 1.5- to 2-fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma, from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

Effect of Food on Absorption of Lamivudine, Zidovudine, and Nevirapine

The effect of food on the rate and extent of absorption of Lamivudine, Zidovudine, and Nevirapine Tablets has not been evaluated. Therefore, Lamivudine, Zidovudine, and Nevirapine Tablets should be taken under fasting conditions.

Specific Populations

Pregnancy

See Use in Specific Populations (8.1).

Lamivudine and Zidovudine tablets: No data are available.

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

Nursing Mothers

See Use in Specific Populations (8.3).

Pediatric Patients

Lamivudine, Zidovudine and Nevirapine Tablets 150/300/200 mg should not be administered to pediatric patients less than 12 years of age or weighing less than 50 kg because it is a fixed-dose combination that cannot be adjusted for this patient population.

Nevirapine

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

BI Trial 1100.1368 studied the safety, efficacy, and pharmacokinetics of a weight-based and a body surface area (BSA)-based dosing regimen of nevirapine. In the weight-based regimen, pediatric subjects up to 8 years of age received a dose of 4 mg/kg once daily for two weeks followed by 7 mg/kg twice daily thereafter. Subjects 8 years and older were dosed 4 mg/kg once daily for two weeks followed by 4 mg/kg twice daily thereafter. In the BSA regimen, all pediatric subjects received 150 mg/m² once daily for two weeks followed by 150 mg/m² twice daily thereafter [see *Use in Specific Populations (8.4) and Adverse Reactions (6.2)*]. Dosing of nevirapine at 150 mg/m² BID (after a two-week lead-in of 150 mg/m² QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 mcg/mL (as targeted from adult data). In addition, the observed trough nevirapine concentrations were comparable between the two dosing regimens studied (BSA- and weightbased methods).

The consolidated analysis of Pediatric AIDS Clinical Trials Group (PACTG) protocols 245, 356, 366, 377, and 403 allowed for the evaluation of pediatric subjects less than 3 months of age (n=17). The plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the pediatric population, but were more variable between subjects, particularly in the second month of age. For dose recommendations for pediatric patients [see *Dosage and Administration (2.2)*].

Geriatric Patients

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Because Lamivudine, Zidovudine and Nevirapine Tablets are a fixed-dose combination, they should not be prescribed for patients who require dose reduction or have renal impairment with CrCL <50 mL/min.

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

Nevirapine: Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with age (range 18–68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 55 years [see *Use in Specific Population (8.5)*].

Gender

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

Nevirapine: In the multinational 2NN 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 the Body Mass Index (BMI) had an influence on the clearance of nevirapine, the effect of gender cannot solely be explained by body size.

Race

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

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

Nevirapine: An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected subjects (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median $C_{\text{minss}} = 4.7$ 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.

Renal Impairment

Because lamivudine and zidovudine require dose adjustment in the presence of renal insufficiency, Lamivudine, Zidovudine and Nevirapine Tablets are not recommended for use in patients with creatinine clearance <50 mL/min [see *Use in Special Populations (8.6)*].

Hepatic Impairment

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Nevirapine should not be administered to patients with severe hepatic impairment. Lamivudine, Zidovudine and Nevirapine Tablets are not recommended for patients with impaired hepatic function because dose adjustments are not possible.

Drug Interactions

See *Drug Interactions (7)*.

No drug interaction studies have been conducted using Lamivudine, Zidovudine and Nevirapine tablets. However, Table 7 presents drug interaction information for 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^a
Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVDINE 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 Coadminister
			AUC	Variability	

					ed Drug
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		Concentratio n of Coadminister ed Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78% ^b	↔
Clarithromycin 500 mg twice daily	100 mg q 4 hr x 7 days	4	↓AUC 12%	Range ↓34% to ↑14%	Not Reported
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64% ^b	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170% ^b	Not Assessed
Rifampin 600 mg daily x 14 days	200 mg q 8 hr X 14 days	8	↓AUC 47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130% ^b	Not Assessed

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

^a This table is not all inclusive.

^b Estimated range of percent difference.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic

(e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected patients [see *Warnings and Precautions* (5.6)].

Nevirapine

Drug Interactions [see Drug Interactions (7.6)]

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

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

Nevirapine does not appear to affect the plasma concentrations of drugs that are substrates of other CYP450 enzyme systems, such as 1A2, 2D6, 2A6, 2E1, 2C9 or 2C19.

Table 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_{max} , and C_{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 Coadministered Drug	Dose Regimen of Nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
				AUC	C_{max}	C_{min}
Antiretrovirals						
Atazanavir/ Ritonavir ^{a,d}	300/100 mg QD day 4–13, then 400/100 mg QD, day 14–23	200 mg BID day 1-23. Subjects were treated with nevirapine prior to trial entry.	23	<u>Atazana vir</u> 300/100 mg	<u>Atazana vir</u> 300/100 mg	<u>Atazana vir</u> 300/100 mg
				↓42 (↓52 to ↓29)	↓28 (↓40 to ↓14)	↓72 (↓80 to ↓60)
				<u>Atazana vir</u> 400/100 mg	<u>Atazana vir</u> 400/100 mg	<u>Atazana vir</u> 400/100 mg
				↓19	↑2	↓59

				(↓35 to ↑2)	(↓15 to ↑24)	(↓73 to ↓40)
Darunavir/Ritonavir ^e	400/100 mg BID	200 mg BID	8	↑24 (↓3 to ↑57)	↑40 (↑14 to ↑73)	↑2 (↓21 to ↑32)
Didanosine	100-150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	§
Efavirenz ^a	600 mg QD	200 mg QD x 14 days; 400 mg QD x 14 days	17	↓28 (↓34 to ↓14)	↓12 (↓23 to ↑1)	↓32 (↓35 to ↓19)
Fosamprenavir	1400 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry.	17	↓33 (↓45 to ↓20)	↓25 (↓37 to ↓10)	↓35 (↓50 to ↓15)
Fosamprenavir/Ritonavir	700/100 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry	17	↓11 (↓23 to ↑3)	↔	↓19 (↓32 to ↓4)
Indinavir ^a	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir ^{a,b}	300/75 mg/m ² (lopinavir/ritonavir) ^b	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15 ^c	↓22 (↓44 to ↑9)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓19)
Lopinavir ^a	400/100 mg BID (lopinavir/ritonavir)	200 mg QD x 14 days; 200 mg BID > 1 year	22, 19 ^c	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Maraviroc ^f	300 mg SD	200 mg BID	8	↑1 (↓35 to ↑55)	↑54 (↓6 to ↑151)	↔

Nelfinavir ^a	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	↔	↔	↓32 (↓50 to ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)
Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	↔
Stavudine	30-40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	↔	↔	§
Zalcitabine	0.125-0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	↔	↔	§
Zidovudine	100-200 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓28 (↓40 to ↓4)	↓30 (↓51 to ↑14)	§
Other Medications				AUC	C_{max}	C_{min}
Clarithromycin ^a	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓31 (↓38 to ↓24)	↓23 (↓31 to ↓14)	↓56 (↓70 to ↓36)
Metabolite 14-OHclarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	↔
Ethinyl estradiol ^a	0.035 mg (as Ortho-Novum® 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	↔	§
and Norethindrone ^a	1 mg (as Ortho-Novum® 1/35)			↓19 (↓30 to ↓7)	↓16 (↓27 to ↓3)	§
Depomedroxyprogesterone acetate	150 mg every 3 months	200 mg QD x 14 days; 200 mg BID x 14 days	32	↔	↔	↔

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

§ = C_{min} below detectable level of the assay

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

^a For information regarding clinical recommendations, see *Drug Interactions (7.6)*.

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

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

^d Parallel group design; n=23 for atazanavir/ritonavir + nevirapine, n=22 for atazanavir/ritonavir without nevirapine. Changes in atazanavir PK are relative to atazanavir/ritonavir 300/100 mg alone.

^e Based on between-trial comparison.

^f Based on historical controls.

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

Administration of rifampin had a clinically significant effect on nevirapine pharmacokinetics, decreasing AUC and C_{\max} by greater than 50%. Administration of fluconazole resulted in an approximate 100% increase in nevirapine exposure, based on a comparison to historic data [see *Drug Interactions (7.6)*]. 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

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

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 polymerase α and γ and has been reported to be incorporated into the DNA of cells in culture.

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

Antiviral Activity

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 μM (1 μM = 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 μM (range: 0.200 to 2.007 μM) from Virco (n = 92 baseline samples from COL40263) and 2.35 μM (1.37 to 3.68 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against

different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM , and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

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 μM (1 μM = 0.27 mcg/mL) and 0.1 to 9 μM , respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.011 μM (range: 0.005 to 0.110 μM) from Virco (n = 92 baseline samples from COL40263) and 0.0017 μM (0.006 to 0.0340 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM , and against HIV-2 isolates from 0.00049 to 0.004 μM . In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, and zalcitabine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Nevirapine: The antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte-derived macrophages, and lymphoblastoid cell lines. In an assay using human embryonic kidney 293 cells, the median EC_{50} value (50% inhibitory concentration) of nevirapine was 90 nM against a panel of 2923 isolates of HIV-1 that were primarily (93%) clade B clinical isolates from the United States. The 99th percentile EC_{50} value was 470 nM in this trial. The median EC_{50} value was 63 nM (range 14-302 nM, n=29) against clinical isolates of HIV-1 clades A, B, C, D, F, G, and H, and circulating recombinant forms CRF01_AE, CRF02_AG and CRF12_BF. Nevirapine had no antiviral activity in cell culture against group 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

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

zidovudine delayed the emergence of amino acid substitutions conferring resistance to zidovudine.

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

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

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.

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

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve patients receiving either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase 1 and 2 trials over 1 to ≥ 12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 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

Cross-resistance has been observed among NRTIs.

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

Lamivudine: See Lamivudine Plus Zidovudine (above).

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) 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 in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), 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.

Nevirapine: Long-term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, 375 or 750 mg/kg/day for two years. Hepatocellular adenomas and carcinomas were increased at all doses in males and at the two high doses in females. In studies in which rats were administered nevirapine at doses of 0, 3.5, 17.5 or 35 mg/kg/day for two years, an increase in hepatocellular adenomas was seen in males at all doses and in females at the high dose. The systemic exposure (based on AUCs) at all doses in the two animal studies were lower than that measured in humans at the 200 mg twice daily dose. The mechanism of the carcinogenic potential is unknown.

Mutagenicity

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

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

Nevirapine: In genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included microbial assays for gene mutation (Ames: Salmonella strains and *E. coli*), mammalian cell gene mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster

ovary cell line and a mouse bone marrow micronucleus assay following oral administration. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is not known.

Impairment of Fertility

Lamivudine: 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.

13.2 Reproductive and Developmental Toxicology Studies

Lamivudine: Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryoletality 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 the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated AUC in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Nevirapine: In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of nevirapine. Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier.

14 CLINICAL STUDIES

14.1 Clinical Studies in Adults

Lamivudine and Zidovudine

There have been no clinical trials conducted with Lamivudine and Zidovudine tablets. See *Clinical Pharmacology (12.3)* for information about bioequivalence. One Lamivudine and zidovudine tablets given twice daily is an alternative regimen to EPIVIR Tablets 150 mg twice daily plus RETROVIR 600 mg per day in divided doses.

The NUCB3007 (CAESAR) study was conducted using EPIVIR 150-mg Tablets (150 mg twice daily) and RETROVIR 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 EPIVIR or EPIVIR 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/mm³ 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)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus a NNRTI ^a plus Current Therapy (n = 460)
HIV-1 progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

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

Nevirapine

Trial BI 1090 was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1 infected subjects with less than 200 CD4⁺ cells/mm³ at screening. Initiated in 1995, BI 1090 compared treatment with Nevirapine + lamivudine + background therapy versus lamivudine + background therapy in NNRTI-naïve subjects. Treatment doses were Nevirapine, 200 mg daily for two weeks followed by 200 mg twice daily or placebo, and lamivudine, 150 mg twice daily. Other antiretroviral agents were given at approved doses. Initial background therapy (in addition to lamivudine) was one NRTI in 1309 subjects (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%). The subjects (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV-1 infection, with a median baseline CD4⁺ cell count of 96 cells/mm³ and a baseline HIV-1 RNA of 4.58 log₁₀ 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 study. 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 ¹ while <50 copies/mL	5	1
Discontinued trial therapy due to AE	7	6
Discontinued trial <48 weeks ²	9	10

¹ including change to open-label nevirapine

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

The change from baseline in CD4⁺ cell count through one year of therapy was significantly greater for the Nevirapine group compared to the placebo group for the overall trial population (64 cells/mm³ vs 22 cells/mm³, respectively), as well as for subjects who entered the trial as treatment-naïve or having received only ZDV (85 cells/mm³ vs 25 cells/mm³, respectively).

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⁺ cell counts of 200-600 cells/mm³ 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 log₁₀ copies/mL (25,704 copies/mL) and mean baseline CD4⁺ cell count of 376 cells/mm³. 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⁺ cell counts in the Nevirapine +ZDV+ddI group increased above baseline by a mean of 139 cells/mm³ at one year, significantly greater than the increase of 87 cells/mm³ in

the ZDV+ddI subjects. The Nevirapine+ZDV group mean decreased by 6 cells/mm³ below baseline.

14.2 Clinical Studies in Pediatric Subjects

Lamivudine and Zidovudine

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⁺ cell counts of 200 to 1,818 cells/mm³ (median in the treated group: 560 cells/mm³) 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.

Nevirapine

The pediatric safety and efficacy of nevirapine was examined in BI Trial 1100.1368, an open-label, randomized clinical trial performed in South Africa in which 123 HIV-1 infected treatment-naïve subjects between 3 months and 16 years of age received Nevirapine oral suspension for 48 weeks. Subjects were divided into 4 age groups (3 months to less than 2 years, 2 to less than 7 years, 7 to less than 12 years, and 12 to less than or equal to 16 years) and randomized to receive one of two Nevirapine doses, determined by 2 different dosing methods [body surface area (150 mg/m²) and weight-based dosing (4 or 7 mg/kg)] in combination with zidovudine and lamivudine [*see Adverse Reactions (6.2), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)*]. The total daily dose of Nevirapine did not exceed 400 mg in either regimen. There were 66 subjects in the body surface area (BSA) dosing group and 57 subjects in the weight-based (BW) dosing group.

Baseline demographics included: 49% male; 81% Black and 19% Caucasian; 4% had previous exposure to ARVs. Subjects had a median baseline HIV-1 RNA of 5.45 log₁₀ copies/mL and a median baseline CD4⁺ cell count of 527 cells/mm³ (range 37 - 2279). One hundred and five (85%) completed the 48-week period while 18 (15%) discontinued prematurely. Of the subjects who discontinued prematurely, 9 (7%) discontinued due to adverse reactions and 3 (2%) discontinued due to virologic failure. Overall the proportion of subjects who achieved and maintained an HIV-1 RNA <400 copies/mL at 48 weeks was 47% (58/123).

For dose recommendations for pediatric patients [*see Dosage and Administration (2)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

Lamivudine, Zidovudine and Nevirapine Tablets 150/300/200 mg, White capsule shaped, biconvex film-coated tablets, debossed with ‘LZN’ on one side and plain on other side. They are available as follows:

30 Tablets/Bottle, 60 Tablets/Bottle & 500 Tablets/Bottle

Store at 15°C - 25°C (59°F - 77°F), [See USP Controlled Room temperature].

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 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 Warnings and Precautions (5.1)*].

17.2 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 Warnings and Precautions (5.2)*].

17.3 Lactic Acidosis/Hepatomegaly

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

17.4 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)*].

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

Lamivudine, Zidovudine and Nevirapine 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)*].

17.6 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)*].

17.7 Hepatotoxicity and Skin Reactions

Inform patients of the possibility of severe liver disease or skin reactions associated with nevirapine that may result in death. Instruct patients developing signs or symptoms of liver disease or severe skin reactions to discontinue Lamivudine, Zidovudine and Nevirapine 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 nevirapine to detect potentially life-threatening hepatotoxicity and skin reactions. However, liver disease can occur after this period; therefore, monitoring should continue at frequent intervals throughout nevirapine treatment. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of hepatic events and skin reactions. Advise patients with signs and symptoms of hepatitis to discontinue Lamivudine, Zidovudine and Nevirapine tablets and seek medical evaluation immediately. If Lamivudine, Zidovudine and Nevirapine tablets is discontinued due to hepatotoxicity, do not restart it. Patients, particularly women, with increased CD4⁺ cell count at initiation of nevirapine therapy (greater than 250 cells/mm³ in women and greater than 400 cells/mm³ in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Advise patients that co-infection with hepatitis B or C and/or increased transaminases at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT [*see Boxed Warning and Warnings and Precautions (5.8)*].

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, Zidovudine and Nevirapine tablets immediately and consult a physician. Lamivudine, Zidovudine and Nevirapine 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 (5.9)*].

17.8 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

nevirapine, since nevirapine may lower the plasma levels of these medications. Additionally, when oral contraceptives are used for hormonal regulation during nevirapine therapy, the therapeutic effect of the hormonal therapy should be monitored [*see Drug Interactions (7.6)*].

17.9 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 (7.6)*].

17.10 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 [*see Drug Interactions (7.3)*]. Lamivudine, Zidovudine and Nevirapine tablets may interact with some drugs, therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort [*see Warnings and Precautions (5.11) and Drug Interactions (7.6)*].

17.11 Fat Redistribution

Inform patients 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 (5.13)*].

17.12 Information About HIV-1 Infection

Lamivudine, Zidovudine and Nevirapine tablets is not a cure for HIV-1 infection; patients may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections. Advise patients to remain under the care of a physician when using Lamivudine, Zidovudine and Nevirapine tablets.

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

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 and zidovudine are excreted in human breast milk. 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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