

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets USP safely and effectively. See full prescribing information for lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets USP.

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets USP, for oral use

### WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATONS OF HEPATITIS B, LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS

See full prescribing information for complete boxed warning.

- Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including lamivudine and tenofovir disoproxil fumarate. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occurs. (5.1)
  - 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 and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
  - Fatal and non-fatal hepatotoxicity (5.10)
  - Fatal and non-fatal skin reactions (5.11)
- Discontinue nevirapine-containing products immediately if experiencing:
- Signs or symptoms of hepatitis (5.10)
  - Increase transaminases combined with rash or other systemic symptoms (5.11)
  - Severe skin or hypersensitivity reactions (5.11)
  - Any rash with systemic symptoms (5.11)
  - Monitoring during the first 18 weeks of therapy is essential. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. (5)

## INDICATIONS AND USAGE

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 300 mg/300 mg Co-packaged with Nevirapine Tablets USP 200 mg, a combination of lamivudine, tenofovir disoproxil fumarate and nevirapine, are indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents 16 years of age and older with a body weight of at least 35 kg. (1)

Important considerations with the use of nevirapine-containing products:

- Initiation of treatment is not recommended in the following populations unless the benefits outweigh the risks (1, 5.10)
  - adult females with CD4<sup>+</sup> cell counts greater than 250 cells/mm<sup>3</sup>
  - adult males with CD4<sup>+</sup> cell counts greater than 400 cells/mm<sup>3</sup>
- The 14-day lead-in period with nevirapine tablets must be strictly followed; it has been demonstrated to reduce the frequency of rash (2.2, 5.11).

## DOSAGE AND ADMINISTRATION

- Lead-in Period (Initial 14 days of dosing): One Lamivudine and Tenofovir Disoproxil Fumarate Tablet with one Nevirapine Tablet (containing 300 mg of lamivudine, 300 mg of tenofovir disoproxil fumarate, and 200 mg of nevirapine) taken once daily orally with or without food (2).
- Maintenance: One Lamivudine and Tenofovir Disoproxil Fumarate Tablet 300 mg/300 mg taken once daily orally and one Nevirapine Tablet 200 mg taken twice daily with or without food. (2)

## DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate, Co-packaged with 200 mg nevirapine. (3)

## CONTRAINDICATIONS

- Patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment. (4.1, 5.10, 8.7)

- Use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens, an unapproved use. (4.2, 5.10)

## WARNINGS AND PRECAUTIONS

- Lactic Acidosis and Hepatomegaly with Steatosis: Reported with the use of nucleoside analogs. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)
- Severe Acute Exacerbations of Hepatitis B: Reported in patients who are co-infected with hepatitis B virus and HIV-1 and have discontinued lamivudine or tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
- Coadministration with Other Products: Do not use with other lamivudine-, emtricitabine-, tenofovir-, or nevirapine-containing products. Do not administer in combination with HEPSERA (adefovir dipivoxil). (5.3)
- New Onset or Worsening Renal Impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating treatment with lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets, monitor CrCl and serum phosphorus in patients at risk. Avoid administering lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine with concurrent or recent use of nephrotoxic drugs. (5.5)
- Decreases in Bone Mineral Density (BMD): Observed in HIV-infected patients. Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.6)
- Immune Reconstitution Syndrome (5.7) and Redistribution/Accumulation of Body Fat (5.8) has been reported in HIV-infected patients receiving antiretroviral combination therapy.
- Triple Nucleoside-only Regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification. (5.9)
- Hepatotoxicity and Hepatic Impairment. (5.10)
- Rash: Fatal and non-fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions, have been reported. Permanently discontinue lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets 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. (5.11)

## ADVERSE REACTIONS

- In HIV-infected adult subjects: Most common adverse reactions are headache, pain, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, rash, depression, asthenia, and cough. (6.1)
- The most common reported adverse reaction 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)

To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

## DRUG INTERACTIONS

- Didanosine: Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Consider dose reductions or discontinuations of didanosine if warranted. (7.4)
- Atazanavir: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.5)
- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.6)
- Coadministration of other drugs may alter the concentrations of nevirapine, one component of lamivudine and tenofovir disoproxil fumarate, co-packaged with nevirapine. The potential for drug-drug interactions must be considered before and during therapy. (5.13, 7.8, 12.3)

## USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Women infected with HIV should be instructed not to breastfeed. (8.3)

---

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B, LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS**

**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Recommended Dose in Adults and Adolescents (Older than 16 Years of Age or Weighing Greater than or Equal to 35 kg)
- 2.2 Dosage Adjustment
- 2.3 Monitoring of Patients

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

- 4.1 Hepatic Impairment
- 4.2 Post-Exposure Prophylaxis

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis
- 5.2 Patients Co-infected with HIV-1 and HBV
- 5.3 Coadministration with Other Products
- 5.4 Use with Interferon- and Ribavirin-Based Regimens
- 5.5 New Onset or Worsening Renal Impairment
- 5.6 Decreases in Bone Mineral Density
- 5.7 Immune Reconstitution Syndrome
- 5.8 Fat Redistribution
- 5.9 Early Virologic Failure
- 5.10 Hepatotoxicity and Hepatic Impairment
- 5.11 Skin Reactions
- 5.12 Resistance
- 5.13 Drug Interactions

**6 ADVERSE REACTIONS**

- 6.1 Adverse Reactions from Clinical Trials Experience
- 6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

- 7.1 Interferon- and Ribavirin-Based Regimens
- 7.2 Trimethoprim/Sulfamethoxazole (TMP/SMX)

- 7.3 Drugs with No Observed Interactions with Lamivudine
- 7.4 Didanosine
- 7.5 Atazanavir
- 7.6 Lopinavir/Ritonavir
- 7.7 Drugs Affecting Renal Function
- 7.8 Drugs Metabolized by Hepatic Cytochrome P450 Isoenzymes, 3A, and 2B6

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Renal Impairment
- 8.7 Patients with Hepatic Impairment

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Reproductive Toxicology Studies and Animal Toxicology and/or Pharmacology

**14 CLINICAL STUDIES**

- 14.1 Clinical Efficacy in Patients with HIV-1 Infection

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

- 17.1 Advice for the Patient
- 17.2 Hepatotoxicity and Skin Reactions
- 17.3 Drug Interactions
- 17.4 Contraceptives
- 17.5 Methadone

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

## FULL PRESCRIBING INFORMATION

### **WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATONS OF HEPATITIS B, LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS**

**Lactic Acidosis and Severe Hepatomegaly:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including lamivudine and tenofovir disoproxil fumarate, two components of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets, in combination with other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur [*see Warnings and Precautions (5.1)*].

**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 human immunodeficiency virus (HIV-1) and have discontinued lamivudine and tenofovir disoproxil fumarate, two components of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are co-infected with HIV-1 and HBV and discontinue lamivudine and tenofovir disoproxil fumarate tablets. If appropriate, resumption of anti-hepatitis B therapy may be warranted [*see Warnings and Precautions (5.2)*].

**Hepatotoxicity:** Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with nevirapine, one component of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher CD4<sup>+</sup> cell counts at initiation of therapy place patients at increased risk; women with CD4<sup>+</sup> cell counts greater than 250 cells/mm<sup>3</sup>, including pregnant women receiving nevirapine in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk. However, hepatotoxicity associated with nevirapine use can occur in both genders, all CD4<sup>+</sup> cell counts and at any time during treatment. Hepatic failure has also been reported in patients without HIV taking nevirapine for post-exposure prophylaxis (PEP). Use of nevirapine for occupational and non-occupational PEP is contraindicated [*see Contraindications (4.2)*]. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue nevirapine and seek medical evaluation immediately [*see Warnings and Precautions (5.10)*].

**Skin Reactions:** Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine, one component of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing

signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. Transaminase levels should be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. The 14-day lead-in period with nevirapine 200 mg daily dosing has been observed to decrease the incidence of rash and must be followed [see *Warnings and Precautions (5.11)*].

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

## 1 INDICATIONS AND USAGE

Lamivudine and Tenofovir Disoproxil Co-packaged with Nevirapine are indicated alone or in combination with other antiretrovirals for the treatment of HIV-1 infection in adults and adolescents 16 years of age and older with a body weight of at least 35 kg (77 lb).

Lamivudine and Tenofovir Disoproxil Fumarate: Lamivudine and Tenofovir Disoproxil Fumarate are nucleoside reverse transcriptase inhibitors indicated in combination with other antiretrovirals for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with lamivudine and tenofovir disoproxil fumarate for the treatment of HIV-1 infection:

- It is not recommended that Lamivudine and Tenofovir disoproxil fumarate Tablets be used as a component of a triple nucleoside regimen.
- They should not be coadministered with ATRIPLA (efavirenz, emtricitabine, and tenofovir disoproxil fumarate), EMTRIVA (emtricitabine), TRUVADA (emtricitabine and tenofovir disoproxil fumarate), VIREAD (tenofovir disoproxil fumarate), HEPSERA (adefovir dipivoxil) or lamivudine-containing products including EPIVIR (lamivudine), EPIVIR-HBV (lamivudine), COMBIVIR (lamivudine and zidovudine), EPZICOM (abacavir sulfate and lamivudine), COMPLERA (rilpivirine, emtricitabine, tenofovir disoproxil fumarate), STRIBILD (cobicistat, elvitegravir, emtricitabine, and tenofovir disoproxil fumarate), and TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine) [See *Warnings and Precautions (5.3)*].

Nevirapine: Nevirapine is a non-nucleoside reverse transcriptase inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

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

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled

trials, nevirapine tablets, USP should not be initiated in adult females with CD4<sup>+</sup> cell counts greater than 250 cells/mm<sup>3</sup> or in adult males with CD4<sup>+</sup> cell counts greater than 400 cells/mm<sup>3</sup> unless the benefit outweighs the risk [*see Boxed Warning and Warnings and Precautions (5.10)*].

- The 14-day lead-in period with nevirapine tablets USP, 200 mg daily dosing must be strictly followed; it has been demonstrated to reduce the frequency of rash [*see Dosage and Administration (2.1) and Warnings and Precautions (5.11)*].
- If rash persists beyond the 14-day lead-in period, do not dose escalate to 200 mg twice daily. The 200 mg once-daily dosing regimen should not be continued beyond 28 days, at which point an alternative regimen should be sought.
- It should not be administered with other nevirapine-containing products, including VIRAMUNE (nevirapine).

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Recommended Dose in Adults and Adolescents [16 Years of Age and Older with a Body Weight of at Least 35 kg (77 lb)]**

#### **Lead-in Period (Initial 14 days of dosing)**

One lamivudine and tenofovir disoproxil fumarate tablet with one nevirapine tablet (containing 300 mg of lamivudine, 300 mg of tenofovir disoproxil fumarate, and 200 mg of nevirapine) taken once daily orally with or without food.

#### **Maintenance**

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

One Lamivudine and Tenofovir Disoproxil Fumarate Tablet 300 mg/300 mg taken once daily orally with or without food and one Nevirapine 200 mg Tablet taken twice daily orally with or without food.

### **2.2 Dose Adjustment**

Because Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets contain a fixed-dose combination formulation, they are not recommended for patients with impaired renal function (creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis.

#### **Nevirapine**

##### *Patients with Rash*

**Discontinue nevirapine if a patient experiences severe rash or any rash accompanied by constitutional findings [see Boxed Warning, Warnings and Precautions (5.11)]. Do not increase nevirapine dose if a patient experiences mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg/day until the rash has resolved [see Warnings and Precautions (5.11)]. The total duration of the once daily lead-in dosing period should not exceed 28 days at which point an alternative regimen should be sought.**

#### *Patients with Hepatic Events*

**If a clinical (symptomatic) hepatic event occurs, permanently discontinue nevirapine. Do not restart nevirapine after recovery [see Warnings and Precautions (5.10)].**

#### *Patients with Dose Interruption*

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

### **2.3 Monitoring of Patients**

#### **Nevirapine**

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

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

#### **Lamivudine and Tenofovir Disoproxil Fumarate**

Lamivudine and Tenofovir Disoproxil Fumarate are available as tablets. Each tablet contains 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients. The tablets are blue colored, oval shaped, beveled edge, biconvex, film-coated tablets, debossed with 'J' on one side and '27' on the other side.

#### **Nevirapine**

Nevirapine tablets USP, 200 mg are white to off-white, oval shape, biconvex tablets, one side

debossed with “C” and “35”, with a single bisect separating “C” and “35.” The other side has a single bisect.

## 4 CONTRAINDICATIONS

### 4.1 Hepatic Impairment

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets are contraindicated in patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.7)*].

### 4.2 Post-Exposure Prophylaxis

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets are contraindicated for use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens [*see Warnings and Precautions (5.10)*].

## 5 WARNINGS AND PRECAUTIONS

### Nevirapine

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

**The first 18 weeks of therapy with nevirapine are a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life-threatening hepatic events and skin reactions.** The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, include monitoring of liver enzyme tests at baseline, prior to dose escalation and at two weeks post-dose escalation. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment. In addition, the 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash [*see Dosage and Administration (2.1)*].

### 5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including lamivudine and tenofovir disoproxil fumarate, two components of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets, in combination with 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 nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with lamivudine and tenofovir disoproxil fumarate 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).

## 5.2 Patients Co-infected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Discontinuation of anti-HBV therapy, including Lamivudine and Tenofovir Disoproxil Fumarate may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue lamivudine and tenofovir disoproxil fumarate should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

Important Differences Among Lamivudine-Containing Products: Lamivudine Tablets contain a higher dose of the same active ingredient (lamivudine) than EPIVIR-HBV Tablets. EPIVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

If treatment with EPIVIR-HBV or tenofovir disoproxil fumarate-containing product such as VIREAD is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment.

Emergence of Lamivudine-Resistant HBV: In non-HIV-1-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.

## 5.3 Coadministration with Other Products

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets USP should not be administered concomitantly with other lamivudine-containing, emtricitabine-containing, tenofovir disoproxil fumarate-containing, or nevirapine-containing products including EPIVIR or EPIVIR-HBV (lamivudine), COMBIVIR (lamivudine and zidovudine), EPZICOM (abacavir sulfate and lamivudine), TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine), ATRIPLA (efavirenz, emtricitabine, and tenofovir disoproxil fumarate), EMTRIVA (emtricitabine), VIREAD (tenofovir disoproxil fumarate), TRUVADA (emtricitabine and

tenofovir disoproxil fumarate), COMPLERA (rilpivirine, emtricitabine, and tenofovir disoproxil fumarate), STRIBILD (cobicistat, elvitegravir, emtricitabine, and tenofovir disoproxil fumarate), and VIRAMUNE (nevirapine). Also, they should not be administered in combination with HEPSERA<sup>®</sup> (adefovir dipivoxil) [see *Drug Interactions* (7.7)].

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

*In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogs such as lamivudine, one component of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients [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 should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh >6). See the complete prescribing information for interferon and ribavirin.

#### **5.5 New Onset or Worsening Renal Impairment**

Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate, a component of lamivudine and tenofovir disoproxil fumarate [see *Adverse Reactions* (6.2)].

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate, a component of lamivudine, and tenofovir disoproxil fumarate tablets. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA<sup>®</sup> (adefovir dipivoxil).

Tenofovir disoproxil fumarate, one component of lamivudine, and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets, should be avoided with concurrent or recent use of a nephrotoxic agent.

#### **5.6 Decreases in Bone Mineral Density**

Assessment of bone mineral density (BMD) should be considered for adults and pediatric patients 12 years of age and older who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

## Adult Patients

In HIV-1 infected adult subjects treated with tenofovir disoproxil fumarate, one component of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets, in Study 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the trial. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate + lamivudine + efavirenz ( $-2.2\% \pm 3.9$ ) compared with subjects receiving stavudine + lamivudine + efavirenz ( $-1\% \pm 4.6$ ). Changes in BMD at the hip were similar between the two treatment groups ( $-2.8\% \pm 3.5$  in the tenofovir disoproxil fumarate group vs.  $-2.4\% \pm 4.5$  in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the tenofovir disoproxil fumarate group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1, 25 Vitamin D levels were also higher in the tenofovir disoproxil fumarate group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range.

The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir disoproxil fumarate [*see Adverse Reactions (6.2)*].

### 5.7 Immune Reconstitution Syndrome

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

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

### 5.8 Fat Redistribution

In HIV-infected patients, 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 combination antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

## 5.9 Early Virologic Failure

Clinical studies in HIV-1 infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

## 5.10 Hepatotoxicity and Hepatic Impairment

Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with nevirapine, one component of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets. In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of subjects who received nevirapine and 1% of subjects in control groups.

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

**Transaminases should be checked immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Transaminases should also be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. The diagnosis of hepatotoxicity should be considered in**

**this setting, even if transaminases are initially normal or alternative diagnoses are possible [see Boxed Warning, Dosage and Administration (2.3), and Patient Counseling Information (17.2)].**

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

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

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-1 uninfected individuals receiving multiple doses of nevirapine in the setting of post-exposure prophylaxis (PEP), an unapproved use. Use of nevirapine for occupational and non-occupational PEP is contraindicated [see *Contraindications (4.2)*].

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 (4.1)*, *Use in Specific Populations (8.7)*, and *Clinical Pharmacology (12.3)*].

## **5.11 Skin Reactions**

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

Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions

(including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue nevirapine and seek medical evaluation immediately [see *Boxed Warning and Patient Counseling Information (17.2)*]. Do not restart nevirapine following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

If patients present with a suspected nevirapine-associated rash, measure transaminases immediately. Permanently discontinue nevirapine in patients with rash-associated transaminase elevations [see *Warnings and Precautions (5.10)*].

Therapy with nevirapine must be initiated with a 14-day lead-in period of 200 mg/day, which has been shown to reduce the frequency of rash. Discontinue nevirapine if a patient experiences severe rash or any rash accompanied by constitutional findings. Do not increase nevirapine dose to a patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg/day until the rash has resolved. The total duration of the once-daily lead-in dosing period must not exceed 28 days at which point an alternative regimen should be sought [see *Dosage and Administration (2.2)*]. Patients must be monitored closely if isolated rash of any severity occurs. Delay in stopping nevirapine treatment after the onset of rash may result in a more serious reaction.

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

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

## **5.12 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)*].

## **5.13 Drug Interactions**

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

Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products and nevirapine is not recommended. Co-administration of St. John's wort with non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine, is expected to

substantially decrease NNRTI concentrations and may result in sub-optimal levels of nevirapine and lead to loss of virologic response and possible resistance to nevirapine or to the class of NNRTIs. Co-administration of nevirapine and efavirenz is not recommended as this combination has been associated with an increase in adverse reactions and no improvement in efficacy.

## 6 ADVERSE REACTIONS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis [*see Boxed Warning, Warnings and Precautions (5.1)*].
- Severe Acute Exacerbations of Hepatitis B [*see Boxed Warning, Warnings and Precautions (5.2)*].
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C [*see Warnings and Precautions (5.4)*].
- New Onset or Worsening Renal Impairment [*see Warnings and Precautions (5.6)*].
- Decreases in Bone Mineral Density [*see Warnings and Precautions (5.7)*].
- Immune Reconstitution Syndrome [*see Warnings and Precautions (5.8)*].
- Hepatic Reaction [*see Warnings and Precautions (5.10)*].
- Skin Reaction [*see Warnings and Precautions (5.11)*].

### 6.1 Adverse reactions from Clinical Trials Experience

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

#### Lamivudine

Clinical Trials in Adult Patients with HIV-1 Infection: The safety profile of lamivudine in adults is primarily based on 3,568 HIV-1-infected patients in 7 clinical trials.

The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea and cough.

*Pancreatitis:* Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received EPIVIR in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and NUCB3007.

*Lamivudine 300 mg Once Daily:* The types and frequencies of clinical adverse reactions reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) for 48 weeks were similar.

The frequencies of selected laboratory abnormalities reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar.

## Tenofovir Disoproxil Fumarate

### Clinical Trials in Adult Patients with HIV-1 Infection

More than 12,000 subjects have been treated with tenofovir disoproxil fumarate alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access studies. A total of 1,544 subjects have received tenofovir disoproxil fumarate 300 mg once daily in clinical trials; over 11,000 subjects have received tenofovir disoproxil fumarate in expanded access programs.

The most common adverse reactions (incidence greater than or equal to 10%, Grades 2 to 4) identified from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

*Treatment-Naïve Patients Study 903 - Treatment-Emergent Adverse Reactions:* The most common adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve subjects received tenofovir disoproxil fumarate (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were mild to moderate gastrointestinal events and dizziness.

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse reactions are summarized in Table 1.

**Table 1. Selected Treatment-Emergent Adverse Reactions<sup>a</sup> (Grades 2 to 4) Reported in  $\geq 5\%$  in Any Treatment Group in Study 903 (0 to 144 Weeks)**

	Tenofovir Disoproxil Fumarate + 3TC + Efavirenz	d4T + 3TC + Efavirenz
	N=299	N=301
<b>Body as a Whole</b>		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal pain	7%	12%
Back pain	9%	8%
Asthenia	6%	7%
<b>Digestive System</b>		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
<b>Metabolic Disorders</b>		
Lipodystrophy <sup>b</sup>	1%	8%
<b>Musculoskeletal</b>		
Arthralgia	5%	7%
Myalgia	3%	5%

<b>Nervous System</b>		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy <sup>c</sup>	1%	5%
Anxiety	6%	6%
<b>Respiratory</b>		
Pneumonia	5%	5%
<b>Skin and Appendages</b>		
Rash event <sup>d</sup>	18%	12%

<sup>a</sup> Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

<sup>b</sup> Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.

<sup>c</sup> Peripheral neuropathy includes peripheral neuritis and neuropathy.

<sup>d</sup> Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

**Laboratory Abnormalities:** With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with tenofovir disoproxil fumarate (19% and 1%) respectively, laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 2.

**Table 2. Grade 3/4 Laboratory Abnormalities Reported in  $\geq 1\%$  of Tenofovir Disoproxil Fumarate-Treated Subjects in Study 903 (0 to 144 Weeks)**

	Tenofovir Disoproxil Fumarate + 3TC + Efavirenz	d4T + 3TC + Efavirenz
	N=299	N=301
Any $\geq$ Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol ( $>240$ mg/dL)	19%	40%
Creatine Kinase (M: $>990$ U/L; F: $>845$ U/L)	12%	12%
Serum Amylase ( $>175$ U/L)	9%	8%
AST (M: $>180$ U/L; F: $>170$ U/L)	5%	7%
ALT (M: $>215$ U/L; F: $>170$ U/L)	4%	5%
Hematuria ( $>100$ RBC/HPF)	7%	7%
Neutrophils ( $<750/\text{mm}^3$ )	3%	1%
Fasting Triglycerides ( $>750$ mg/dL)	1%	9%

### Treatment-Experienced Patients

**Treatment-Emergent Adverse Reactions:** The adverse reactions seen in treatment experienced subjects were generally consistent with those seen in treatment naïve subjects including mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of subjects discontinued participation in the clinical studies due to gastrointestinal adverse reactions (Study 907).

A summary of moderate to severe, treatment-emergent adverse reactions that occurred during the first 48 weeks of Study 907 is provided in Table 3.

**Table 3. Selected Treatment-Emergent Adverse Reactions<sup>a</sup> (Grades 2 to 4) Reported in  $\geq 3\%$  in Any Treatment Group in Study 907 (0 to 48 Weeks)**

	<b>Tenofovir Disoproxil Fumarate (N=368) (Week 0 to 24)</b>	<b>Placebo (N=182) (Week 0 to 24)</b>	<b>Tenofovir Disoproxil Fumarate (N=368) (Week 0 to 48)</b>	<b>Placebo Crossover to Tenofovir Disoproxil Fumarate (N=170) (Week 24 to 48)</b>
<b>Body as a Whole</b>				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal pain	4%	3%	7%	6%
Back pain	3%	3%	4%	2%
Chest pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
<b>Digestive System</b>				
Diarrhea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
<b>Respiratory</b>				
Pneumonia	2%	0%	3%	2%
<b>Nervous System</b>				
Depression	4%	3%	8%	4%
Insomnia	3%	2%	4%	4%
Peripheral neuropathy <sup>b</sup>	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
<b>Skin and Appendage</b>				
Rash event <sup>c</sup>	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
<b>Musculoskeletal</b>				
Myalgia	3%	3%	4%	1%
<b>Metabolic</b>				
Weight loss	2%	1%	4%	2%

<sup>a</sup>. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

<sup>b</sup>. Peripheral neuropathy includes peripheral neuritis and neuropathy.

<sup>c</sup>. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesicubullous rash, and pustular rash.

**Laboratory Abnormalities:** Laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 4.

**Table 4. Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate-Treated Subjects in Study 907 (0 to 48 Weeks)**

	<b>Tenofovir disoproxil fumarate (N=368) (Week 0 to 24)</b>	<b>Placebo (N=182) (Week 0 to 24)</b>	<b>Tenofovir disoproxil fumarate (N=368) (Week 0 to 48)</b>	<b>Placebo Crossover to Tenofovir disoproxil fumarate (N=170) (Week 24 to 48)</b>
Any ≥ Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Glycosuria (≥3+)	3%	3%	3%	2%
AST (M: >180 U/L; F: >170 U/L)	3%	3%	4%	5%
ALT (M: >215 U/L; F: >170 U/L)	2%	2%	4%	5%
Serum Glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750/mm <sup>3</sup> )	1%	1%	2%	1%

## ***Nevirapine***

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

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

The most serious adverse reactions associated with nevirapine are hepatitis, hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction [*see Boxed Warning and Warnings and Precautions (5.10, 5.11)*].

### ***Hepatic Reaction***

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of subjects who received nevirapine and 1% of subjects in control groups. Female gender and higher CD4<sup>+</sup> cell counts (greater than 250 cells/mm<sup>3</sup> in women and greater than 400 cells/mm<sup>3</sup> in men) place patients at increased risk of these events [*see Boxed Warning and Warnings and Precautions (5.10)*].

Asymptomatic transaminase elevations (AST or ALT greater than 5x ULN) were observed in 6% (range 0% to 9%) of subjects who received nevirapine and 6% of subjects in control groups. Co-infection with hepatitis B or C and/or increased transaminase elevations at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more

after starting nevirapine) and asymptomatic increases in AST or ALT.

Liver enzyme abnormalities (AST, ALT, GGT) were observed more frequently in subjects receiving nevirapine than in controls see Table 6.

### *Skin Reaction*

The most common clinical toxicity of nevirapine is rash, which can be severe or life-threatening [see *Boxed Warning and Warnings and Precautions (5.11)*]. Rash occurs most frequently within the first 6 weeks of therapy. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. In controlled clinical trials (Trials 1037, 1038, 1046, and 1090), Grade 1 and 2 rashes were reported in 13% of subjects receiving nevirapine compared to 6% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 2% of nevirapine recipients compared to less than 1% of subjects receiving placebo. Women tend to be at higher risk for development of nevirapine-associated rash [see *Boxed Warning and Warnings and Precautions (5.11)*].

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 5.

**Table 5. Percentage of Subjects with Moderate or Severe Drug-Related Events in Adult Placebo-Controlled Trials**

	Trial 1090 <sup>1</sup>		Trials 1037, 1038, 1046 <sup>2</sup>	
	Nevirapine (n=1121)	Placebo (n=1128)	Nevirapine (n=253)	Placebo (n=203)
Median exposure (weeks)	58	52	28	28
Any adverse event	15%	11%	32%	13%
Rash	5	2	7	2
Nausea	1	1	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

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

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

### *Laboratory Abnormalities*

Liver enzyme test abnormalities (AST, ALT) were observed more frequently in subjects receiving nevirapine than in controls (Table 6). 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 6.

**Table 6. Percentage of Adult Subjects with Laboratory Abnormalities**

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

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

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

## 6.2 Postmarketing Experience

The following adverse reactions have been reported during postmarketing use of lamivudine, tenofovir disoproxil fumarate, nevirapine. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine, tenofovir disoproxil fumarate, and nevirapine.

### Lamivudine

*Body as a Whole:* Redistribution/accumulation of body fat [see Warnings and Precautions (5.8)].

*Endocrine and Metabolic:* Hyperglycemia.

*General:* Weakness.

*Hemic and Lymphatic:* Anemia (including pure red cell aplasia and severe anemias progressing on therapy).

*Hepatic and Pancreatic:* Lactic acidosis and hepatic steatosis, posttreatment exacerbation of hepatitis B [see Boxed Warning, Warnings and Precautions (5.1, 5.2)].

*Hypersensitivity:* Anaphylaxis, urticaria.

*Musculoskeletal:* Muscle weakness, CPK elevation, rhabdomyolysis.

*Skin:* Alopecia, pruritus.

## **Tenofovir Disoproxil Fumarate**

*Immune System Disorders:* Allergic reaction, including angioedema

*Metabolism and Nutrition Disorders:* Lactic acidosis, hypokalemia, hypophosphatemia

*Respiratory, Thoracic, and Mediastinal Disorders:* Dyspnea

*Gastrointestinal Disorders:* Pancreatitis, increased amylase, abdominal pain

*Hepatobiliary Disorders:* Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

*Skin and Subcutaneous Tissue Disorders:* Rash

*Musculoskeletal and Connective Tissue Disorders:* Rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

*Renal and Urinary Disorders:* Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria [see *Warnings and Precautions (5.5)*].

*General Disorders and Administration Site Conditions:* Asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

## **Nevirapine**

*Body as a Whole:* fever, somnolence, drug withdrawal [see *Drug Interactions (7)*], redistribution/accumulation of body fat [see *Warnings and Precautions (5.8)*]

*Gastrointestinal:* vomiting

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

*Hematology:* anemia, eosinophilia, neutropenia

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

## **7 DRUG INTERACTIONS**

No drug interaction studies have been conducted using lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets. Drug interaction studies have been conducted with the individual components: lamivudine, tenofovir disoproxil fumarate, and nevirapine [*see Clinical Pharmacology (12.3)*].

### **Lamivudine**

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

#### **7.1 Interferon- and Ribavirin-Based Regimens**

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin [*see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)*].

#### **7.2 Trimethoprim/Sulfamethoxazole (TMP/SMX)**

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

#### **7.3 Drugs with No Observed Interactions with Lamivudine**

A drug interaction study showed no clinically significant interaction between lamivudine and zidovudine.

### **Tenofovir Disoproxil Fumarate**

#### **7.4 Didanosine**

Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When administered with tenofovir disoproxil fumarate, the  $C_{max}$  and AUC of didanosine (administered as either the buffered or enteric-coated formulation) increased significantly [*see Clinical Pharmacology (12.3)*]. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of  $CD4^+$  cell counts has been observed in patients receiving tenofovir disoproxil fumarate (tenofovir DF) with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with tenofovir DF. In patients weighing less than 60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with tenofovir DF. When coadministered, tenofovir disoproxil fumarate and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). For additional information on coadministration of tenofovir DF and didanosine, please refer to the full prescribing information for didanosine.

## 7.5 Atazanavir

Atazanavir has been shown to increase tenofovir concentrations [*see Clinical Pharmacology (12.3)*]. The mechanism of this interaction is unknown. Patients receiving atazanavir and tenofovir disoproxil fumarate should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir Disoproxil Fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

Tenofovir Disoproxil Fumarate decreases the AUC and  $C_{min}$  of atazanavir [*see Clinical Pharmacology (12.3)*]. When coadministered with tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with tenofovir disoproxil fumarate.

## 7.6 Lopinavir/Ritonavir

Lopinavir/ritonavir has been shown to increase tenofovir concentrations [*see Clinical Pharmacology (12.3)*]. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and tenofovir disoproxil fumarate should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir Disoproxil Fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

## 7.7 Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys [*see Clinical Pharmacology (12.3)*], coadministration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or



Fosamprenavir/Ritonavir*	<p>↓ Amprenavir</p> <p>↑ Nevirapine</p>	No dosing adjustments are required when nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir twice daily. The combination of nevirapine administered with fosamprenavir/ritonavir once daily has not been studied.
Indinavir*	↓ Indinavir	The appropriate doses of this combination of indinavir and nevirapine with respect to efficacy and safety have not been established.
Lopinavir/Ritonavir*	↓ Lopinavir	<p>Dosing in adult patients:</p> <p>A dose adjustment of lopinavir/ritonavir to 500/125 mg tablets twice daily or 533/133 mg (6.5 mL) oral solution twice daily is recommended when used in combination with nevirapine. Neither lopinavir/ritonavir tablets nor oral solution should be administered once daily in combination with nevirapine.</p>
Nelfinavir*	<p>↓ Nelfinavir M8 Metabolite</p> <p>↓ Nelfinavir C<sub>min</sub></p>	The appropriate doses of the combination of nevirapine and nelfinavir with respect to safety and efficacy have not been established.
Saquinavir/ritonavir	The interaction between nevirapine and saquinavir/ritonavir has not been evaluated	The appropriate doses of the combination of nevirapine and saquinavir/ritonavir with respect to safety and efficacy have not been established.
<b>HIV Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b>		
Efavirenz*	↓ Efavirenz	The appropriate doses of these combinations with respect to safety and efficacy have not been established.
Delavirdine Etravirine Rilpivirine		Plasma concentrations may be altered. Nevirapine should not be coadministered with another NNRTI as this combination has not

---

been shown to be beneficial.

---

**Other Agents**

---

**Analgesics:**  
Methadone\*

↓ Methadone

Methadone levels were decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

---

**Antiarrhythmics:**

Amiodarone, disopyramide, lidocaine

Plasma concentrations may be decreased.

Appropriate doses for this combination have not been established.

---

**Antibiotics:**

Clarithromycin\*

↓ Clarithromycin  
↑ 14-OH clarithromycin

Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex*, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.

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.
<b>Anticonvulsants:</b> Carbamazepine, clonazepam, ethosuximide	Plasma concentrations of nevirapine and the anticonvulsant may be decreased.	Use with caution and monitor virologic response and levels of anticonvulsants.
<b>Antifungals:</b> 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.
Ketoconazole*	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Itraconazole	↓ Itraconazole	Nevirapine and itraconazole should not be administered concomitantly due to potential decreases in itraconazole plasma concentrations that may reduce efficacy of the drug.
<b>Antithrombotics:</b> Warfarin	Plasma concentrations may be increased.	Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.
<b>Calcium channel blockers:</b> Diltiazem, nifedipine, verapamil	Plasma concentrations may be decreased.	Appropriate doses for these combinations have not been established.
<b>Cancer chemotherapy:</b> Cyclophosphamide	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
<b>Ergot alkaloids:</b> Ergotamine	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.

<b>Immunosuppressants:</b> Cyclosporine, tacrolimus, sirolimus	Plasma concentrations may be decreased.	Appropriate doses for these combinations have not been established.
<b>Motility agents:</b> Cisapride	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
<b>Opiate agonists:</b> Fentanyl	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
<b>Oral contraceptives:</b> 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.

\* The interaction between nevirapine and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Lamivudine, Tenofovir Disoproxil Fumarate and Nevirapine

Lamivudine is classified under category C. Tenofovir disoproxil and nevirapine are classified under category B. There are no adequate and well-controlled studies of the combination of lamivudine and tenofovir disoproxil fumarate co-packaged with nevirapine in pregnant women. Lamivudine and tenofovir disoproxil fumarate tablets co-packaged nevirapine tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**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. These studies were not designed or powered to provide efficacy information.

Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant

adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, lamivudine amniotic fluid specimens were collected following natural rupture of membranes. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily). It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients.

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 embryo lethality 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)*].

**Tenofovir Disoproxil Fumarate: Animal Data:** Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

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

**Animal Data:** 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).

### 8.3 Nursing Mothers

**Lamivudine and Tenofovir Disoproxil Fumarate Co-packaged with Nevirapine:** 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 and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets.

**Lamivudine:** Lamivudine is excreted into human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

**Tenofovir Disoproxil Fumarate:** Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is excreted in human milk at low levels. The impact of this exposure in breastfed infants is unknown.

#### 8.4 Pediatric Use

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets should only be administered to HIV-1 patients 16 years of age and older with a body weight of at least 35 kg (77 lb). Because this co-packaged product contains a fixed-dose combination formulation, it cannot be adjusted for patients of lower age and weight. Safety and efficacy have not been established in pediatric patients less than 16 years of age with a body weight less than 35 kg.

#### 8.5 Geriatric Use

**Lamivudine and Tenofovir Disoproxil Fumarate Tablets Co-packaged with Nevirapine Tablets:** Clinical studies with the individual components: lamivudine, tenofovir disoproxil fumarate, 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 the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

#### 8.6 Patients with Renal Impairment

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-package Nevirapine Tablets are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because they contain a fixed-dose combination formulation that cannot be adjusted.

#### 8.7 Patients with Hepatic Impairment

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged Nevirapine Tablets are not recommended for patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [*see Contraindications (4.1), Warnings and Precautions (5.10), and Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

**Lamivudine:** There is no known antidote for 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.

**Tenofovir Disoproxil Fumarate:** Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

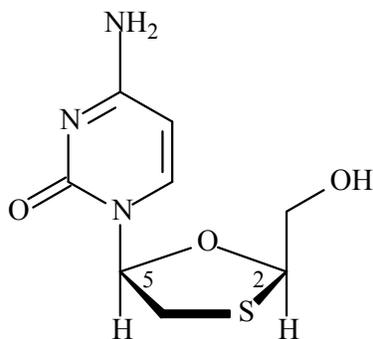
**Nevirapine:** There is no known antidote for nevirapine overdosage. Cases of nevirapine overdose at doses ranging from 800 to 1800 mg per day for up to 15 days have been reported. Patients have experienced events including edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary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

## 11 DESCRIPTION

Lamivudine and Tenofovir Disoproxil Fumarate Tablets are for oral administration. Each tablet contains 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, as active ingredients. The tablets also include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, FD&C Blue#2, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Lamivudine and Tenofovir Disoproxil Fumarate Tablets are fixed-dose combination tablets containing lamivudine and tenofovir disoproxil fumarate. Lamivudine (also known as 3TC) belongs to the synthetic nucleoside analog class of antiretroviral drugs. Tenofovir disoproxil fumarate (a prodrug of tenofovir) is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Both lamivudine and tenofovir disoproxil fumarate exhibit inhibitory activity against HIV-1 reverse transcriptase.

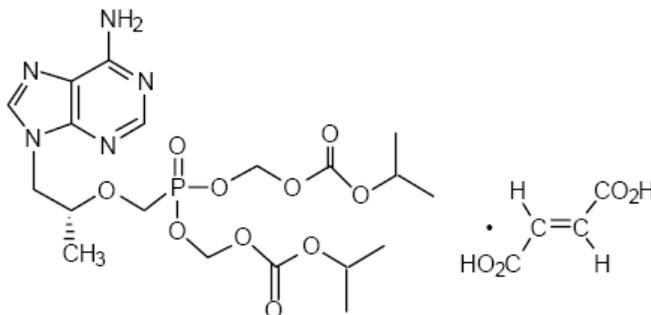
**Lamivudine:** The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of C<sub>8</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S and a molecular weight of 229.3. It has the following structural formula:



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

**Tenofovir Disoproxil Fumarate:** Tenofovir disoproxil fumarate is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir.

The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2-[[bis[[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of  $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$  and a molecular weight of 635.52. It has the following structural formula:

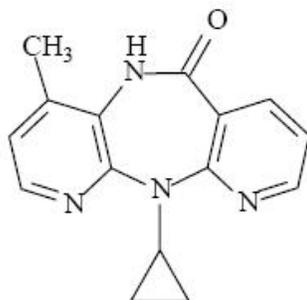


Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25°C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient ( $\log p$ ) of 1.25 at 25°C.

In this insert, all dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

**Nevirapine:** Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Nevirapine is structurally a member of the 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 USP 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:



Nevirapine tablets, USP are for oral administration. Each tablet contains 200 mg of nevirapine and the inactive ingredients colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

## 12 CLINICAL PHARMACOLOGY

For additional information on Mechanism of Action, Antiviral Activity, Resistance and Cross Resistance, please consult the lamivudine, tenofovir disoproxil fumarate, and nevirapine prescribing information.

### 12.1 Mechanism of Action

Lamivudine and Tenofovir Disoproxil Fumarate tablets, Co-packaged with Nevirapine Tablets are a combination of antiviral drugs: lamivudine, tenofovir disoproxil fumarate, and nevirapine [*see Microbiology (12.4)*].

### 12.3 Pharmacokinetics

#### Pharmacokinetics in Adults

*Lamivudine and Tenofovir Disoproxil Fumarate:* Lamivudine and tenofovir disoproxil fumarate from the combination tablets (300 mg/300 mg) were bioequivalent to that from EPIVIR (lamivudine) Tablets and VIREAD (tenofovir disoproxil fumarate) Tablets respectively, when administered to healthy volunteers under fasted and fed conditions.

*Nevirapine:* Nevirapine tablets (200 mg) were bioequivalent to VIRAMUNE (nevirapine) Tablets, when administered to healthy volunteers under fasted and fed conditions.

#### **Lamivudine**

The steady-state pharmacokinetics properties of the lamivudine 300 mg tablet once daily for 7 days compared with the lamivudine 150 mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma  $AUC_{24,ss}$ ; however,  $C_{max,ss}$  was 66% higher and the trough value was 53% lower compared with the 150 mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to  $AUC_{24,ss}$  and  $C_{max24,ss}$ ; however, trough

values were lower compared with the 150 mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

**Absorption and Bioavailability:** Lamivudine was rapidly absorbed after oral administration in HIV-1-infected patients. Absolute bioavailability in 12 adult patients was  $86\% \pm 16\%$  (mean  $\pm$  SD) for the 150 mg tablet and  $87\% \pm 13\%$  for the oral solution. After oral administration of 2 mg/kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration ( $C_{\max}$ ) was  $1.5 \pm 0.5$  mcg/mL (mean  $\pm$  SD). The area under the plasma concentration versus time curve (AUC) and  $C_{\max}$  increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.

The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1.5 following 15 days of oral administration of 2 mg/kg twice daily.

**Effects of Food on Oral Absorption:** An investigational 25 mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-1-infected patients on 2 occasions, once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state ( $T_{\max}$ :  $3.2 \pm 1.3$  hours) compared with the fasted state ( $T_{\max}$ :  $0.9 \pm 0.3$  hours);  $C_{\max}$  in the fed state was  $40\% \pm 23\%$  (mean  $\pm$  SD) lower than in the fasted state. There was no significant difference in systemic exposure ( $AUC_{\infty}$ ) in the fed and fasted states; therefore, lamivudine tablets may be administered with or without food.

**Distribution:** The apparent volume of distribution after IV administration of lamivudine to 20 patients was  $1.3 \pm 0.4$  L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low ( $<36\%$ ). *In vitro* studies showed that over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

**Metabolism:** Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-1-infected adults,  $5.2\% \pm 1.4\%$  (mean  $\pm$  SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

**Elimination:** The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300 mg oral dose of lamivudine, renal clearance was  $199.7 \pm 56.9$  mL/min (mean  $\pm$  SD). In 20 HIV-1-infected patients given a single IV dose, renal clearance was  $280.4 \pm 75.2$  mL/min (mean  $\pm$  SD), representing  $71\% \pm 16\%$  (mean  $\pm$  SD) of total clearance of lamivudine.

In most single-dose studies in HIV-1-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life

( $t_{1/2}$ ) ranged from 5 to 7 hours. In HIV-1-infected patients, total clearance was  $398.5 \pm 69.1$  mL/min (mean  $\pm$  SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

### **Tenofovir Disoproxil Fumarate**

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

**Absorption:** Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted subjects is approximately 25%. Following oral administration of a single dose of tenofovir disoproxil fumarate 300 mg to HIV-1 infected subjects in the fasted state, maximum serum concentrations ( $C_{max}$ ) are achieved in  $1 \pm 0.4$  hrs.  $C_{max}$  and AUC values are  $0.30 \pm 0.09$  mcg/mL and  $2.29 \pm 0.69$  mcg•hr/mL, respectively.

The pharmacokinetics of tenofovir are dose proportional over a tenofovir disoproxil fumarate dose range of 75 to 600 mg and are not affected by repeated dosing.

**Distribution:** *In vitro* binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 mcg/mL. The volume of distribution at steady-state is  $1.3 \pm 0.6$  L/kg and  $1.2 \pm 0.4$  L/kg, following intravenous administration of tenofovir 1 mg/kg and 3 mg/kg.

**Metabolism and Elimination:** *In vitro* studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.

Following IV administration of tenofovir, approximately 70 to 80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir disoproxil fumarate 300 mg once daily (under fed conditions),  $32 \pm 10\%$  of the administered dose is recovered in urine over 24 hours.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

**Effects of Food on Oral Absorption:** Administration of tenofovir disoproxil fumarate following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir  $AUC_{0-\infty}$  of approximately 40% and an increase in  $C_{max}$  of approximately 14%. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir  $C_{max}$  by approximately 1 hour.  $C_{max}$  and AUC of tenofovir are  $0.33 \pm 0.12$  mcg/mL and  $3.32 \pm 1.37$  mcg•hr/mL

following multiple doses of tenofovir disoproxil fumarate 300 mg once daily in the fed state, when meal content was not controlled.

## **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  $2 \pm 0.4$  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  $4.5 \pm 1.9$  mcg/mL ( $17 \pm 7$  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<sup>®</sup> 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<sub>t</sub>) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without food, antacid or didanosine.

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

**Metabolism/Elimination:** *In vivo* 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 <sup>14</sup>C-nevirapine, approximately  $91.4 \pm 10.5\%$  of the radiolabeled dose was recovered, with urine ( $81.3 \pm 11.1\%$ ) representing the primary route of excretion compared to feces ( $10.1 \pm 1.5\%$ ). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (less than 5%) of the radioactivity in urine (representing less than 3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

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

**Effect of Food on Absorption of Lamivudine and Tenofovir Disoproxil Fumarate Tablets Co-packaged with Nevirapine Tablets:** Lamivudine and tenofovir disoproxil fumarate combination tablets (300 mg/300 mg) were bioequivalent to EPIVIR (lamivudine) Tablets and VIREAD (tenofovir disoproxil fumarate) Tablets and Nevirapine tablets (200 mg) were bioequivalent to VIRAMUNE (nevirapine) Tablets, when administered to healthy volunteers under in the fasted and fed conditions states. Therefore, this co-packaged product can be administered with or without food.

## Special Populations

### Race

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

**Tenofovir Disoproxil Fumarate:** There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

**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.

### Pediatric Patients

Lamivudine and Tenofovir Disoproxil Fumarate tablets co-packaged with Nevirapine tablets should not be administered to HIV-1 infected pediatric patients less than 16 years of age with a body weight of less than 35 kg (77 lb).

**Geriatric Patients:** Lamivudine and Tenofovir Disoproxil Fumarate: The pharmacokinetics of lamivudine and tenofovir disoproxil fumarate have not been studied in patients over 65 years of age have not been studied [*see Use in Specific Populations (8.5)*].

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

## **Gender**

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

**Tenofovir Disoproxil Fumarate:** *Tenofovir pharmacokinetics are similar in male and female subjects.*

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

## **Patients with Renal Impairment**

*See Use in Specific Populations* (8.6).

**Lamivudine and Tenofovir Disoproxil Fumarate Co-packaged with Nevirapine** are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because they contain a fixed-dose combination formulation that cannot be adjusted.

## **Patients with Hepatic Impairment**

**Lamivudine and Tenofovir Disoproxil Fumarate Co-packaged with Nevirapine** is contraindicated for patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [see *Contraindications* (4), *Warnings and Precautions* (5.10), and *Use in Specific Populations* (8.7)].

**Nevirapine:** In a steady-state trial comparing 46 subjects with mild (n=17; expansion of some portal areas; Ishak Score 1 to 2), moderate (n=20; expansion of most portal areas with occasional portal-to-portal and portal-to-central bridging; Ishak Score 3 to 4), or severe (n=9; marked bridging with occasional cirrhosis without decompensation indicating Child-Pugh A; Ishak Score 5 to 6) fibrosis as a measure of hepatic impairment, the multiple dose pharmacokinetic disposition of nevirapine and its five oxidative metabolites were not altered. However, approximately 15% of these subjects with hepatic fibrosis had nevirapine trough concentrations above 9,000 mcg/mL (2-fold the usual mean trough). Therefore, patients with hepatic impairment should be monitored carefully for evidence of drug-induced toxicity [see *Warnings and Precautions* (5.1)]. The subjects studied were receiving antiretroviral therapy containing nevirapine 200 mg twice daily for at least 6 weeks prior to pharmacokinetic sampling, with a median duration of therapy of 3.4 years.

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

### **Assessment of Drug Interactions**

*See Drug Interactions (7).*

No drug interaction studies have been conducted using lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets.

**Lamivudine:** *Interferon Alfa:* There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects [see *Warnings and Precautions (5.4)*].

*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 (5.4)*].

*Trimethoprim/Sulfamethoxazole:* Lamivudine and TMP/SMX were coadministered to 14 HIV-1-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300 mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design.

Coadministration of TMP/SMX with lamivudine resulted in an increase of  $43\% \pm 23\%$  (mean  $\pm$  SD) in lamivudine  $AUC_{\infty}$ , a decrease of  $29\% \pm 13\%$  in lamivudine oral clearance, and a decrease of  $30\% \pm 36\%$  in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine [see *Drug Interactions (7.2)*].

*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) [see *Drug Interactions (7.3)*].

**Tenofovir Disoproxil Fumarate:** At concentrations substantially higher (~300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed.

Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP mediated interactions involving tenofovir disoproxil fumarate with other medicinal products is low.

Tenofovir Disoproxil Fumarate has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 8 and 9 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug. Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of Coadministration of tenofovir disoproxil fumarate with didanosine significantly increases the C<sub>max</sub> and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions (Table 9). The mechanism of this interaction is unknown.

No clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and efavirenz, methadone, nelfinavir, oral contraceptives, or ribavirin.

**Table 8. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir<sup>a</sup> in the Presence of the Coadministered Drug**

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters <sup>b</sup> (90% CI)		
			C <sub>max</sub>	AUC	C <sub>min</sub>
Abacavir	300 once	8	↔	↔	NC
Atazanavir <sup>c</sup>	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine <sup>d</sup>	250 or 400 once daily × 7 days	14	↔	↔	↔
Emtricitabine	200 once daily × 7 days	17	↔	↔	↔
Entecavir	1 mg once daily × 10 days	28	↔	↔	↔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↔	↔	↔
Lopinavir/Ritonavir	400/100 twice daily × 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/Ritonavir	1000/100 twice daily × 14 days	35	↔	↔	↑ 23 (↑ 16 to ↑ 30)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔

<sup>a</sup> Subjects received tenofovir disoproxil fumarate 300 mg once daily.

<sup>b</sup> Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated

<sup>c</sup> Reyataz (atazanavir) Prescribing Information

<sup>d</sup> Subjects received didanosine buffered tablets.

**Table 9. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate**

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters <sup>a</sup> (90% CI)		
			C <sub>max</sub>	AUC	C <sub>min</sub>
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Atazanavir <sup>b</sup>	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir <sup>b</sup>	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25 <sup>c</sup> (↓ 42 to ↓ 3)	↓ 23 <sup>c</sup> (↓ 46 to ↑ 10)
Didanosine <sup>d</sup>	250 once, simultaneously with tenofovir disoproxil fumarate and a light meal <sup>e</sup>	33	↓ 20 <sup>f</sup> (↓ 32 to ↓ 7)	⇔	NA
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily × 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔	⇔	⇔
Ritonavir			⇔	⇔	⇔
Saquinavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29 <sup>g</sup> (↑ 12 to ↑ 48)	↑ 47 <sup>g</sup> (↑ 23 to ↑ 76)
Ritonavir			⇔	⇔	↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	⇔	⇔	⇔

<sup>a</sup> Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable

<sup>b</sup> Reyataz (atazanavir) Prescribing Information

<sup>c</sup> In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C<sub>min</sub> values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

<sup>d</sup> Videx EC (didanosine) Prescribing Information. Subjects received didanosine enteric-coated capsules.

<sup>e</sup> 373 kcal, 8.2

<sup>f</sup> Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.

<sup>g</sup> Increases in AUC and  $C_{min}$  are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution [See Drug Interactions (7.4)]. When administered with multiple doses of tenofovir disoproxil fumarate, the  $C_{max}$  and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

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

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

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

Table 10 (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 10. Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Nevirapine (All interactions trials were conducted in HIV-1 positive subjects)**

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of Nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
				AUC	$C_{max}$	$C_{min}$
<b>Antiretrovirals</b>						
Atazanavir/Ritonavir <sup>a, d</sup>	300/100 mg QD day 4 to 13, then 400/ 100 mg QD, day 14 to 23	200 mg BID day 1 to 23. Subjects were treated with nevirapine prior to trial entry.	23	<u>Atazanavir</u> <u>300/100 mg</u>	<u>Atazanavi</u> <u>r 300/100</u> <u>mg</u>	<u>Atazanavi</u> <u>r 300/100</u> <u>mg</u>
				↓42 (↓52 to ↓29)	↓28 (↓40 to ↓14)	↓72 (↓80 to ↓60)
				<u>Atazanavir</u> <u>400/100 mg</u>	<u>Atazanavi</u> <u>r 400/100</u> <u>mg</u>	<u>Atazanavi</u> <u>r 400/100</u> <u>mg</u>

				↓19 (↓35 to ↑2)	↑2 (↓15 to ↑24)	↓59 (↓73 to ↓40)
Darunavir/Ritonavir <sup>e</sup>	400/100 mg BID	200 mg BID	8	↑24 (↓3 to ↑57)	↑40 (↑14 to ↑73)	↑2 (↓21 to ↑32)
Didanosine	100 to 150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	§
Efavirenz <sup>a</sup>	600 mg QD	200 mg QD x 14 days; 400 mg QD x 14 days	17	↓28 (↓34 to ↓14)	↓12 (↓23 to ↑1)	↓32 (↓35 to ↓19)
Fosamprenavir	1400 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry.	17	↓33 (↓45 to ↓20)	↓25 (↓37 to ↓10)	↓35 (↓50 to ↓15)
Fosamprenavir/Ritonavir	700/100 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry	17	↓11 (↓23 to ↑3)	↔	↓19 (↓32 to ↓4)
Indinavir <sup>a</sup>	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir <sup>a, b</sup>	300/75 mg/m <sup>2</sup> (lopinavir/ritonavir) <sup>b</sup>	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15 <sup>c</sup>	↓22 (↓44 to ↑9)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓19)
Lopinavir <sup>a</sup>	400/100 mg BID (lopinavir/ritonavir)	200 mg QD x 14 days; 200 mg BID >1 year	22, 19 <sup>c</sup>	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Maraviroc <sup>f</sup>	300 mg SD	200 mg BID	8	↑1 (↓35 to ↑55)	↑54 (↓6 to ↑151)	↔
Nelfinavir <sup>a</sup>	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	↔	↔	↓32 (↓50 to ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)
Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	↔
Stavudine	30 to 40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	↔	↔	§

Zalcitabine	0.125 to 0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	↔	↔	§
Zidovudine	100 to 200 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓28 (↓40 to ↓4)	↓30 (↓51 to ↑14)	§
<b>Other Medications</b>				<b>AUC</b>	<b>C<sub>max</sub></b>	<b>C<sub>min</sub></b>
Clarithromycin <sup>a</sup>	500 mg BID	200 mg QD x 14 days;	15	↓31 (↓38 to ↓24)	↓23 (↓31 to ↓14)	↓56 (↓70 to ↓36)
Metabolite 14-OH-clarithromycin		200 mg BID x 14 days		↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	↔
Ethinyl estradiol <sup>a</sup> and Norethindrone <sup>a</sup>	0.035 mg (as Ortho-Novum <sup>®</sup> 1/35)  1 mg (as Ortho-Novum <sup>®</sup> 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	↔	§
				↓19 (↓30 to ↓7)	↓16 (↓27 to ↓3)	§
Depomedroxy-progesterone acetate	150 mg every 3 months	200 mg QD x 14 days; 200 mg BID x 14 days	32	↔	↔	↔
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↔	↔	↔
Ketoconazole <sup>a</sup>	400 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	21	↓72 (↓80 to ↓60)	↓44 (↓58 to ↓27)	§
Methadone <sup>a</sup>	Individual Subject Dosing	200 mg QD x 14 days; 200 mg BID ≥7 days	9	In a controlled pharmacokinetic trial with 9 subjects receiving chronic methadone to whom steady-state nevirapine therapy was added, the clearance of methadone was increased by 3-fold, resulting in symptoms of withdrawal, requiring dose adjustments in 10 mg segments, in 7 of the 9 subjects. Methadone did not have any effect on nevirapine clearance.		
Rifabutin <sup>a</sup>	150 or 300 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↑17 (↓2 to ↑40)	↑28 (↑9 to ↑51)	↔
Metabolite				↑24	↑29	↑22

25-O-desacetyl-rifabutin				(↓16 to ↑84)	(↓2 to ↑68)	(↓14 to ↑74)
Rifampin <sup>a</sup>	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑11 (↓4 to ↑28)	↔	§

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

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

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

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

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

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

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

<sup>f</sup> Based on historical controls.

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

Administration of rifampin had a clinically significant effect on nevirapine pharmacokinetics, decreasing AUC and C<sub>max</sub> by greater than 50%. Administration of fluconazole resulted in an approximate 100% increase in nevirapine exposure, based on a comparison to historic data [*see Drug Interactions (7)*]. The effect of other drugs listed in Table 10 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 nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA polymerases  $\alpha$ ,  $\beta$ , and  $\gamma$ .

**Tenofovir Disoproxil Fumarate:** Tenofovir Disoproxil Fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir Disoproxil Fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV polymerase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases  $\alpha$ ,  $\beta$ , and mitochondrial DNA polymerase  $\gamma$ .

**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  $\alpha$ ,  $\beta$ ,  $\gamma$ , or  $\delta$ ) are not inhibited by nevirapine.

## Antiviral Activity

**Lamivudine:** The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays.  $EC_{50}$  values (50% effective concentrations) were in the range of 0.003 to 15  $\mu\text{M}$  (1  $\mu\text{M}$  = 0.23 mcg/mL). HIV-1 from therapy-naïve subjects with no amino acid substitutions associated with resistance gave median  $EC_{50}$  values of 0.429  $\mu\text{M}$  (range: 0.2 to 2.007  $\mu\text{M}$ ) from Virco (n = 92 baseline samples from COLA40263) and 2.35  $\mu\text{M}$  (1.37 to 3.68  $\mu\text{M}$ ) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The  $EC_{50}$  values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.12  $\mu\text{M}$ , and against HIV-2 isolates from 0.003 to 0.12  $\mu\text{M}$  in peripheral blood mononuclear cells. Ribavirin (50  $\mu\text{M}$ ) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. Please see the full prescribing information for EPIVIR-HBV (lamivudine) for information regarding the inhibitory activity of lamivudine against HBV.

**Tenofovir Disoproxil Fumarate:** The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The  $EC_{50}$  (50% effective concentration) values for tenofovir were in the range of 0.04  $\mu\text{M}$  to 8.5  $\mu\text{M}$ . In drug combination studies, tenofovir was not antagonistic with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir). Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O ( $EC_{50}$  values ranged from 0.5  $\mu\text{M}$  to 2.2  $\mu\text{M}$ ) and strain specific activity against HIV-2 ( $EC_{50}$  values ranged from 1.6  $\mu\text{M}$  to 5.5  $\mu\text{M}$ ).

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

nevirapine was antagonized by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin in cell culture.

## Resistance

**Lamivudine:** Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine 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 mutations conferring resistance to zidovudine.

Lamivudine-resistant HBV isolates develop substitutions (rtM204V/I) in the YMDD motif of the catalytic domain of the viral reverse transcriptase. rtM204V/I substitutions are frequently accompanied by other substitutions (rtV173L, rtL180M) which enhance the level of lamivudine resistance or act as compensatory mutations improving replication efficiency. Other substitutions detected in lamivudine-resistant HBV isolates include: rtL80I and rtA181T. Similar HBV mutants have been reported in HIV-1-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus [*see Warnings and Precautions (5.2)*].

**Tenofovir Disoproxil Fumarate:** HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2 to 4 fold reduction in susceptibility to tenofovir.

In Study 903 of treatment-naïve subjects (tenofovir disoproxil fumarate + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz) [*see Clinical Studies (14.1)*], genotypic analyses of isolates from subjects with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) analyzed patient isolates on the tenofovir disoproxil fumarate arm and in 2/49 (4%) analyzed patient isolates on the stavudine arm. Of the 8 subjects whose virus developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and one at Week 96. Other substitutions resulting in resistance to tenofovir disoproxil fumarate were not identified in this trial.

In Study 934 of treatment-naïve subjects (tenofovir disoproxil fumarate + emtricitabine + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz) [*see Clinical Studies (14.1)*], genotypic analysis performed on HIV-1 isolates from all confirmed virologic failure subjects

with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation showed development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the two treatment arms. The M184V substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 analyzed subject isolates in the tenofovir disoproxil fumarate + emtricitabine group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

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

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve subjects receiving either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase 1 and 2 trials over 1 to  $\geq 12$  weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 subjects had decreased susceptibility to nevirapine in cell culture. One or more of the RT mutations resulting in amino acid substitutions K103N, V106A, V108I, Y181C, Y188C, and G190A were detected in HIV-1 isolates from some subjects as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the subjects tested (n=24) had HIV-1 isolates with a greater than 100-fold decrease in susceptibility to nevirapine in cell culture compared to baseline, and had one or more of the nevirapine-associated RT resistance substitutions. Nineteen of these subjects (80%) had isolates with Y181C substitutions regardless of dose.

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

### **Cross-Resistance**

**Lamivudine:** Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI). In some patients treated with zidovudine plus didanosine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates From Patients With Virologic Failure: *Study EPV20001:* Fifty-three of 554 (10%) subjects enrolled in EPV20001 were identified as virological failures (plasma HIV-1 RNA level  $\geq 400$  copies/mL) by Week 48. Of the 53 failures, 28 subjects were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA levels of subjects in the lamivudine once-daily group and lamivudine twice-daily group were 4.9  $\log_{10}$  copies/mL and 4.6  $\log_{10}$  copies/mL, respectively. Genotypic analysis of on-therapy isolates from 22 subjects identified as virologic failures in the lamivudine once-daily group showed:

- isolates from 0/22 subjects contained treatment-emergent zidovudine resistance-associated amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E)
- isolates from 10/22 subjects contained treatment-emergent efavirenz resistance-associated amino acid substitutions (L100I, K101E, K103N, V108I, or Y181C)
- isolates from 8/22 subjects contained a treatment-emergent lamivudine resistance-associated amino acid substitution (M184I or M184V)

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from subjects (n =13) receiving lamivudine once daily showed:

- isolates from 12/13 subjects were susceptible to zidovudine
- isolates from 8/13 subjects exhibited a 25- to 295-fold decrease in susceptibility to efavirenz
- isolates from 7/13 subjects showed an 85- to 299-fold decrease in susceptibility to lamivudine

**Study EPV40001:** Fifty subjects received zidovudine 300 mg twice daily plus abacavir 300 mg twice daily plus lamivudine 300 mg once daily and 50 subjects received zidovudine 300 mg plus abacavir 300 mg plus lamivudine 150 mg all twice daily. The median baseline plasma HIV-1 RNA levels for subjects in the 2 groups were 4.79 log<sub>10</sub> copies/mL and 4.83 log<sub>10</sub> copies/mL, respectively. Fourteen of 50 subjects in the lamivudine once-daily treatment group and 9 of 50 subjects in the lamivudine twice-daily group were identified as virologic failures.

Genotypic analysis of on-therapy HIV-1 isolates from subjects (n = 9) in the lamivudine once-daily treatment group showed that isolates from 6 subjects had an abacavir and/or lamivudine resistance-associated substitution M184V alone. On-therapy isolates from subjects (n = 6) receiving lamivudine twice daily showed that isolates from 2 subjects had M184V alone, and isolates from 2 subjects harbored the M184V substitution in combination with zidovudine resistance-associated amino acid substitutions.

Phenotypic analysis of on-therapy isolates from subjects (n = 6) receiving lamivudine once daily showed that HIV-1 isolates from 4 subjects exhibited a 32- to 53-fold decrease in susceptibility to lamivudine. HIV-1 isolates from these 6 subjects were susceptible to zidovudine.

**Tenofovir Disoproxil Fumarate:** Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R substitution selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV-1 isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R substitution. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir.

In Studies 902 and 907 conducted in treatment-experienced subjects (tenofovir disoproxil fumarate + Standard Background Therapy (SBT) compared to Placebo + SBT), 14/304 (5%) of the tenofovir disoproxil fumarate-treated subjects with virologic failure through Week 96 had

greater than 1.4-fold (median 2.7-fold) reduced susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R substitution in the HIV-1 reverse transcriptase gene.

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment-experienced subjects participating in Studies 902 and 907. In these clinical trials, 94% of the participants evaluated had baseline HIV-1 isolates expressing at least one NRTI mutation. Virologic responses for subjects in the genotype substudy were similar to the overall trial results.

Several exploratory analyses were conducted to evaluate the effect of specific substitutions and substitutional patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross-resistance of tenofovir disoproxil fumarate to pre-existing zidovudine resistance-associated substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) were observed and appeared to depend on the type and number of specific substitutions. Tenofovir disoproxil fumarate-treated subjects whose HIV-1 expressed 3 or more zidovudine resistance-associated substitutions that included either the M41L or L210W reverse transcriptase substitution showed reduced responses to tenofovir disoproxil fumarate therapy; however, these responses were still improved compared with placebo. The presence of the D67N, K70R, T215Y/F, or K219Q/E/N substitution did not appear to affect responses to tenofovir disoproxil fumarate therapy. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to tenofovir disoproxil fumarate. Limited data are available for subjects whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

In the protocol defined analyses, virologic response to tenofovir disoproxil fumarate was not reduced in subjects with HIV-1 that expressed the abacavir/emtricitabine/lamivudine resistance-associated M184V substitution. HIV-1 RNA responses among these subjects were durable through Week 48.

### **Studies 902 and 907 Phenotypic Analyses**

Phenotypic analysis of baseline HIV-1 from treatment-experienced subjects (N=100) demonstrated a correlation between baseline susceptibility to tenofovir disoproxil fumarate and response to tenofovir disoproxil fumarate therapy. Table 11 summarizes the HIV-1 RNA response by baseline tenofovir disoproxil fumarate susceptibility.

**Table 11. HIV-1 RNA Response at Week 24 by Baseline Tenofovir Disoproxil Fumarate Susceptibility (Intent-To-Treat)<sup>a</sup>**

<b>Baseline Tenofovir Disoproxil Fumarate Susceptibility<sup>b</sup></b>	<b>Change in HIV-1 RNA<sup>c</sup> (N)</b>
<1	-0.74 (35)
>1 and ≤3	-0.56 (49)
>3 and ≤4	-0.3 (7)
>4	-0.12 (9)

- <sup>a</sup>. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).
- <sup>b</sup>. Fold change in susceptibility from wild-type.
- <sup>c</sup>. Average HIV-1 RNA change from baseline through Week 24 (DAVG<sub>24</sub>) in log<sub>10</sub> copies/mL.

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

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**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. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

**Tenofovir Disoproxil Fumarate:** Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir Disoproxil Fumarate was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

**Nevirapine:** Long-term carcinogenicity studies in mice and rats were carried out with

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

### 13.2 Reproductive 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.

### 13.2 Animal Toxicology and/or Pharmacology

**Tenofovir Disoproxil Fumarate:** Tenofovir and Tenofovir Disoproxil Fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

**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 Efficacy in Patients with HIV-1 Infection

#### *Lamivudine and Tenofovir Disoproxil Fumarate*

##### *Treatment-Naïve Adult Patients*

##### *Study 903*

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter trial comparing tenofovir disoproxil fumarate (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve subjects. Subjects had a mean age of 36 years (range 18 to 64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4<sup>+</sup> cell count was 279 cells/mm<sup>3</sup> (range 3 to 956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417 to 5,130,000). Subjects were stratified by baseline HIV-1 RNA and CD4<sup>+</sup> cell count. Forty-three percent of subjects had baseline viral loads >100,000 copies/mL and 39% had CD4<sup>+</sup> cell counts <200 cells/mm<sup>3</sup>. Treatment outcomes through 48 and 144 weeks are presented in Table 12.

**Table 12. Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)**

Outcomes	At Week 48		At Week 144	
	Tenofovir Disoproxil Fumarate+ 3TC+EFV (N=299)	d4T+3TC +EFV (N=301)	Tenofovir Disoproxil Fumarate+ 3TC+EFV (N=299)	d4T+3TC +EFV (N=301)
Responder*	79%	82%	68%	62%
Virologic failure <sup>†</sup>	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons <sup>‡</sup>	8%	7%	14%	15%

\* Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.

<sup>†</sup> Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.

<sup>‡</sup> Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and CD4<sup>+</sup> cell count (< or ≥200 cells/mm<sup>3</sup>). Through 144 weeks of therapy, 62% and 58% of subjects in the tenofovir disoproxil fumarate and stavudine arms, respectively achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4<sup>+</sup> cell count was 263 cells/mm<sup>3</sup> for the

tenofovir disoproxil fumarate arm and 283 cells/mm<sup>3</sup> for the stavudine arm.

Through 144 weeks, 11 subjects in the tenofovir disoproxil fumarate group and 9 subjects in the stavudine group experienced a new CDC Class C event.

### ***Nevirapine***

Trial BI 1090 was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1 infected subjects with less than 200 CD4<sup>+</sup> cells/mm<sup>3</sup> at screening. Initiated in 1995, BI 1090 compared treatment with nevirapine + lamivudine + background therapy versus lamivudine + background therapy in NNRTI-naïve subjects. Treatment doses were nevirapine, 200 mg daily for two weeks followed by 200 mg twice daily or placebo, and lamivudine, 150 mg twice daily. Other antiretroviral agents were given at approved doses. Initial background therapy (in addition to lamivudine) was one NRTI in 1309 subjects (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%). The subjects (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV-1 infection, with a median baseline CD4<sup>+</sup> cell count of 96 cells/mm<sup>3</sup> and a baseline HIV-1 RNA of 4.58 log<sub>10</sub> copies/mL (38,291 copies/mL). Prior to entering the trial, 45% had previously experienced an AIDS-defining clinical event. Eighty-nine percent had antiretroviral treatment prior to entering the trial. BI 1090 was originally designed as a clinical endpoint trial. Prior to unblinding the trial, the primary endpoint was changed to proportion of subjects with HIV-1 RNA less than 50 copies/mL and not previously failed at 48 weeks. Treatment response and outcomes are shown in Table 13.

**Table 13. BI 1090 Outcomes Through 48 Weeks**

<b>Outcome</b>	<b>Nevirapine (N=1121) %</b>	<b>Placebo (N=1128) %</b>
Responders at 48 weeks: HIV-1 RNA <50 copies/mL	18	2
Treatment Failure	82	98
Never suppressed viral load	45	66
Virologic failure after response	7	4
CDC category C event or death	10	11
Added antiretroviral therapy <sup>1</sup> while <50 copies/mL	5	1
Discontinued trial therapy due to AE	7	6
Discontinued trial <48 weeks <sup>2</sup>	9	10

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

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

The change from baseline in CD4<sup>+</sup> 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/mm<sup>3</sup> vs. 22 cells/mm<sup>3</sup>, respectively), as well as for subjects who entered the trial as treatment-naïve or having received only ZDV (85 cells/mm<sup>3</sup> vs. 25 cells/mm<sup>3</sup>, 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<sup>+</sup> cell counts of 200 to 600 cells/mm<sup>3</sup> at baseline. BI 1046 compared treatment with nevirapine+zidovudine+didanosine to nevirapine+zidovudine and zidovudine+didanosine. Treatment doses were nevirapine at 200 mg daily for two weeks followed by 200 mg twice daily or placebo, zidovudine at 200 mg three times daily, and didanosine at 125 or 200 mg twice daily (depending on body weight). The subjects had mean baseline HIV-1 RNA of 4.41 log<sub>10</sub> copies/mL (25,704 copies/mL) and mean baseline CD4<sup>+</sup> cell count of 376 cells/mm<sup>3</sup>. The primary endpoint was the proportion of subjects with HIV-1 RNA less than 400 copies/mL and not previously failed at 48 weeks. The virologic responder rates at 48 weeks were 45% for subjects treated with nevirapine+zidovudine+didanosine, 19% for subjects treated with zidovudine+didanosine, and 0% for subjects treated with nevirapine+zidovudine.

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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

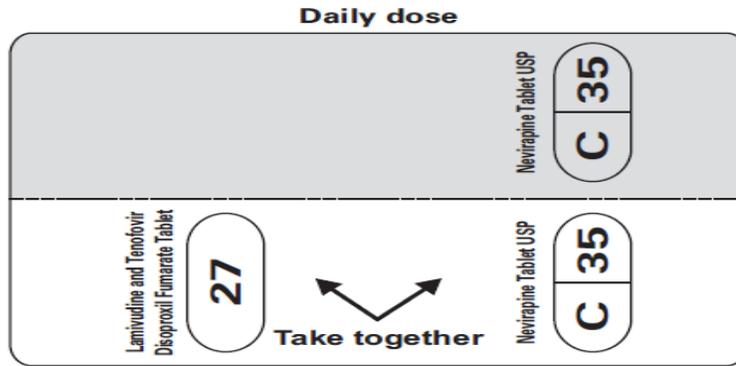
**Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg** are available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil and 300 mg of lamivudine USP. The tablets are Blue colored, oval shaped, beveled edge, biconvex, film-coated tablets debossed with ‘J’ on one side and ‘27’ on the other side.

**Nevirapine Tablets USP 200 mg** are white to off-white, oval shaped, biconvex tablets, one side debossed with “C” and “35” with a single bisect separating “C” and “35.” The other side has a single biset.

**Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg Co-packaged with Nevirapine Tablets USP 200 mg** are supplied in cartons containing 15 blister packs for a 30 day supply. Each blister pack contains two 1-day cards. Each 1-day card contains two Nevirapine tablets USP 200 mg and one Lamivudine and Tenofovir disoproxil fumarate tablet 300 mg/300 mg.

30 day supply blister pack

NDC 65862-755-09



Store below 30°C (86°F).

## 17 PATIENT COUNSELING INFORMATION

- “See FDA-approved patient labeling (Medication Guide)”

### 17.1 Advice for the Patient

Patients should be advised that:

- Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets are not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets.
- Patients should 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 to lower the chance of sexual contact with semen, vaginal secretions, or blood.
  - **Do not breastfeed.** Lamivudine, tenofovir disoproxil fumarate, and nevirapine 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.
- The long term effects of lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets are unknown.
- Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets are for oral ingestion only.
- Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets should not be discontinued without first informing their physician.
- It is important to take lamivudine and tenofovir disoproxil fumarate tablets, co-packaged

with nevirapine tablets on a regular dosing schedule and to avoid missing doses.

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) [*see Warnings and Precautions (5.1)*].
- Severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or co-infected with HBV and HIV-1 and have discontinued lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets [*see Warnings and Precautions (5.2)*].
- 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 (5.4)*].
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets should be avoided with concurrent or recent use of a nephrotoxic agent. Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis [*see Dosage and Administration (2.2)*].
- Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets should not be administered in combination with HEPSERA (adefovir dipivoxil) [*see Warnings and Precautions (5.3)*].
- Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets should not be coadministered with other lamivudine-containing, emtricitabine-containing, nevirapine-containing drugs or tenofovir-containing, including COMBIVIR (lamivudine and zidovudine), EPIVIR or EPIVIR-HBV (lamivudine), EPZICOM (abacavir sulfate and lamivudine), or TRIZIVIR (abacavir sulfate, lamivudine and zidovudine), EMTRIVA (emtricitabine), STRIBILD (cobicistat, elvitegravir, emtricitabine, and tenofovir disoproxil fumarate), VIREAD (tenofovir disoproxil fumarate), VIRAMUNE (nevirapine), TRUVADA<sup>®</sup> (emtricitabine and tenofovir disoproxil fumarate), COMPLERA (emtricitabine, rilpivirine and tenofovir) or ATRIPLA (emtricitabine, efavirenz and tenofovir disoproxil fumarate) [*see Warnings and Precautions (5.3)*].
- Decreases in bone mineral density have been observed with the use of lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets in patients with HIV. Bone mineral density monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia [*see Warnings and Precautions (5.6)*].
- Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including lamivudine, nevirapine and tenofovir disoproxil fumarate, and that the cause and long-term health effects of these conditions are not known at this time [*see Warnings and Precautions (5.8)*].

## 17.2 Hepatotoxicity and Skin Reactions

**Inform patients of the possibility of severe liver disease or skin reactions associated with nevirapine-containing products that may result in death. Instruct patients developing signs or symptoms of liver disease or severe skin reactions to discontinue nevirapine 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 nevirapine and seek medical evaluation immediately. If nevirapine is discontinued due to hepatotoxicity, do not restart it. Patients, particularly women, with increased CD4<sup>+</sup> cell count at initiation of nevirapine therapy (greater than 250 cells/mm<sup>3</sup> in women and greater than 400 cells/mm<sup>3</sup> in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Advise patients that co-infection with hepatitis B or C and/or increased transaminases at the start of therapy 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 (5.10)*].

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 nevirapine immediately and consult a physician. Nevirapine should not be restarted following severe skin rash or hypersensitivity reaction. Women tend to be at higher risk for development of nevirapine-associated rash [*see Boxed Warning and Warnings and Precautions (5.11)*].

### **17.3 Drug Interactions**

Nevirapine, one component of Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with 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.

### **17.4 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, one component of lamivudine and tenofovir disoproxil fumarate tablets co-packaged

with nevirapine tablets, 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)*].

### **17.5 Methadone**

Nevirapine, one component of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets, 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)*].

All brands listed are the trademarks of their respective owners and are not trademarks of Aurobindo Pharma Limited.

Manufactured for:

**Aurobindo Pharma USA, Inc.**

2400 Route 130 North

Dayton, NJ 08810

Manufactured by:

**Aurobindo Pharma Limited**

Unit-VII (SEZ)

Mahaboob Nagar (Dt)

AP-509302, INDIA

Issued: October 2013

## MEDICATION GUIDE

### **Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 300 mg/300 mg Co-packaged with Nevirapine Tablets USP, 200 mg**

Read this Medication Guide before you start taking lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

#### **What is the Most Important Information I Should Know About Lamivudine and Tenofovir Disoproxil Fumarate Tablets Co-packaged with Nevirapine Tablets?**

**Nevirapine, one component of Lamivudine and Tenofovir Disoproxil Fumarate Tablets Co-packaged with Nevirapine Tablets, can cause serious side effects. These include severe liver and skin problems that can cause death. These problems can happen at any time during treatment, but your risk is higher during the first 18 weeks of treatment.**

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

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

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

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

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

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

You may get a rash if you have liver problems.

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

- dark (tea colored) urine
- yellowing of your skin or whites of your eyes
- light-colored bowel movements (stools)
- fever

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

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

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

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

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

See the section "**What are the possible side effects of Lamivudine and Tenofovir Disoproxil Fumarate Tablets Co-packaged with Nevirapine Tablets?**" for more information.

Patients taking lamivudine and tenofovir disoproxil fumarate, two components of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets, may develop:

**3. Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take lamivudine, tenofovir disoproxil fumarate, or similar (nucleoside analog) medicines. **Lactic acidosis** is a serious medical emergency that can lead to death.

Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get the following symptoms which could be signs of lactic acidosis:**

- feeling very weak or tired
- have unusual (not normal) muscle pain

- have trouble breathing
  - have stomach pain with
    - nausea (feel sick to your stomach)
    - vomiting
  - feel cold, especially in your arms and legs
  - feel dizzy or lightheaded
  - have a fast or irregular heartbeat
4. Worsening of your Hepatitis B infection. If you have hepatitis B Virus (HBV) infection it may become worse (flare-up) if you take lamivudine and tenofovir disoproxil fumarate tablets, two components of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets, and then stop them. A “flare-up” is when your HBV infection suddenly returns in a worse way than before.
- Do not let your lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine run out.

Refill your prescription or talk to your healthcare provider before your lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine are all gone.

- Do not stop taking lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine without first talking to your doctor.
- If you stop taking lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine, your doctor will need to check your health often and do regular blood tests to check your HBV infection. Tell your doctor about any new or unusual symptoms you may have after you stop taking lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine.

### **What are Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets?**

- Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-Packaged with Nevirapine Tablets can be used alone or in combination with other antiviral medicines to treat Human Immunodeficiency Virus (HIV) in patients 16 years of age and older with a body weight of at least 35 kg (77 pounds). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-Packaged with Nevirapine Tablets are prescription antiviral medicines. Lamivudine and tenofovir disoproxil fumarate are a type of medicines called nucleoside analog reverse transcriptase inhibitors (NRTIs) and nevirapine is a non-nucleoside analog reverse transcriptase inhibitor (NNRTI).

- When used with alone or in combination with other HIV medicines, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-Packaged with Nevirapine Tablets may:

1. Reduce the amount of HIV in your blood (called “viral load”)
2. Help increase the number of CD4 (T) cells in your blood which help fight off other infections.

Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

**Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets do not cure HIV-1 infection or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections.** You should remain under the care of a doctor **while taking lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets.**

You must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

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 or razor blades.**
- **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom or other barrier to reduce the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your doctor if you have any questions on how to prevent passing HIV to other people.

**Who Should Not Take Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets?**

Tell your doctor if you have or have had liver or kidney problems. Your doctor may tell you not to take nevirapine, one component of Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-Packaged with Nevirapine Tablets, if you have certain liver problems.

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-Packaged with Nevirapine Tablets are only for people diagnosed with HIV. If you have not been diagnosed as HIV positive, then do not take Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-Packaged with Nevirapine Tablets.

**What Should I Tell My Doctor Before Taking Lamivudine And Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets?**

**Before you take Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets, tell your doctor if you:**

- Have or have had hepatitis (inflammation of your liver) or problems with your liver. See **“What is the most important information I should know about Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets?”** and **“Who should not take Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets?”**
- Receive dialysis
- Have skin problems, such as rash
- Have any medical conditions
- Are pregnant or planning to become pregnant. It is not known if Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets will harm your unborn baby.
- Are breastfeeding or plan to breast-feed. Lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets can pass into your breast milk and may harm your baby. You should not breastfeed if you have HIV because of the risk of passing HIV to your baby. Do not breast-feed during treatment with Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets. Talk to your doctor about the best way to feed your baby.

**Tell your doctor and pharmacist about all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets may affect the way other medicines work, and other medicines may affect how Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets works.

You should not take Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets if you also take:

- St. John’s Wort. St. John’s Wort can lower the amount of Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets in your body.
- efavirenz (Sustiva<sup>®</sup>) , etravirine (Intelence<sup>®</sup>), rilpivirine (Edurant<sup>®</sup>), or delavirdine (Rescriptor<sup>®</sup>).
- atazanavir (Reyataz<sup>®</sup>)
- lopinavir and ritonavir (Kaletra<sup>®</sup>) once daily
- fosamprenavir calcium (Lexiva<sup>®</sup>) without ritonavir (Norvir<sup>®</sup>)
- itraconazole (Sporanox<sup>®</sup>)
- ketoconazole (Nizoral<sup>®</sup>)
- rifampin (Rifadin<sup>®</sup>, Rifamate<sup>®</sup>, Rifater<sup>®</sup>)
- Birth control pills. Birth control pills taken by mouth (oral contraceptives) and other hormone types of birth control may not work to prevent pregnancy. Talk with your doctor about other types of birth control that you can use to prevent pregnancy during treatment with Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets.
- other medicines that contain tenofovir disoproxil fumarate such as:
  - tenofovir disoproxil fumarate (VIREAD)

- efavirenz, emtricitabine, and tenofovir disoproxil fumarate (ATRIPLA)
- rilpivirine, emtricitabine, and tenofovir disoproxil fumarate (COMPLERA)
- emtricitabine and tenofovir disoproxil fumarate (TRUVADA)
- cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil fumarate (STRIBILD)
- other medicines that contain lamivudine or emtricitabine such as:
  - lamivudine (EPIVIR, EPIVIR-HBV)
  - lamivudine and zidovudine (COMBIVIR)
  - abacavir sulfate and lamivudine (EPZICOM)
  - abacavir sulfate, lamivudine, and zidovudine (TRIZIVIR)
  - emtricitabine (EMTRIVA)
- adefovir (HEPSERA)
- didanosine (VIDEC, VIDEX EC)
- interferon alfa and ribavirin

Also tell your doctor if you take:

- clarithromycin (Biaxin<sup>®</sup>)
- fluconazole (Diflucan<sup>®</sup>)
- indinavir sulfate (Crixivan<sup>®</sup>)
- methadone
- nelfinavir mesylate (Viracept<sup>®</sup>)
- rifabutin (Mycobutin<sup>®</sup>)
- warfarin (Coumadin<sup>®</sup>, Jantoven<sup>®</sup>)
- saquinavir mesylate (Invirase<sup>®</sup>)
- amiodarone, disopyramide (Norpace<sup>®</sup>), lidocaine
- carbamazepine, clonazepam (Klonopin<sup>®</sup>), ethosuximide (Zarontin<sup>®</sup>)
- diltiazem, nifedipine, verapamil
- cyclophosphamide
- ergotamine
- cyclosporine, tacrolimus, sirolimus (Rapamune<sup>®</sup>)
- cisapride (Propulsid<sup>®</sup>)
- fentanyl

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

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

### **How Should I Take Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged With Nevirapine Tablets?**

- Take the medicines in this co-packaged exactly as directed by your doctor. If you do not understand these directions, ask your pharmacist, nurse, or doctor to explain them to you

**Adults and Adolescents 16 years of age and older with a body weight of at least 35 kg (77 pounds)**

- The usual dose of the Lamivudine and Tenofovir Disoproxil Fumarate Tablets (both the medications are present in one single tablet) for adult and adolescents is one tablet taken once a day. The usual dose of the co-packaged nevirapine tablets for adults is one tablet daily for the first 14 days followed by one tablet twice daily thereafter. Starting with one Nevirapine Tablet a day for the first 14 days lowers the chance of rash, which could be serious. Therefore, it is important to strictly follow the once daily dose of nevirapine tablets for the first 14 days. Follow your doctor's instructions.
- Take each dose with a full glass of water.  
These medications are taken with or without food.
- Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged With Nevirapine Tablets are not recommended in patients less than 16 years of age with a body weight less than 35 kg (77 pounds).
- Do not let your Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets run out.
- If you stop taking nevirapine tablets for more than 7 days, ask your doctor before you start taking them again. You may need to begin taking nevirapine starting dose again, which is taken 1 time each day for 14 days.

**Starting nevirapine tablets:**

1. Your doctor should start you with 1 dose each day to lower your chance of getting a serious rash. **It is important that you only take 1 dose of nevirapine each day for the first 14 days.**
  - **Call your doctor right away if you get a skin rash during the first 14 days of nevirapine treatment.**
  - **Do not increase your dose to 2 times a day if you have a rash.**
  - You should never take your starting dose for longer than 28 days. If after 28 days you are still receiving this starting dose because you have a rash, you and your doctor should talk about prescribing another HIV medicine for you instead of nevirapine.
2. Day 15, you will take 1 nevirapine tablet two times a day.
  - Treatment of HIV/AIDS almost always requires the use of all the three drugs. If you need to stop taking one of the medicines you are taking for HIV, you should stop all of them until you can talk to your doctor.
  - Your doctor may want you to have blood tests or other medical evaluations during treatment with this medication to monitor progress and side effects.

**What are the Possible Side Effects of Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets?**

(Also see "**What is the most important information I should know about Lamivudine and Tenofovir Disoproxil Fumarate Tablets Co-packaged with Nevirapine Tablets?**" at the beginning of this Medication Guide).

Lamivudine and Tenofovir Disoproxil Fumarate, two components of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets, may cause other serious side effects, including:

**New or worse kidney problems** can happen in some people who take lamivudine and tenofovir disoproxil fumarate. If you have had kidney problems in the past or need to take another medicine that can cause kidney problems, your healthcare provider may need to do blood tests to check your kidneys during your treatment with lamivudine and tenofovir disoproxil fumarate tablets.

**Bone problems** can happen in some people who take lamivudine and tenofovir disoproxil fumarate. Bone problems include bone pain, softening or thinning (which may lead to fractures). Your healthcare provider may need to do additional tests to check your bones.

The most common side effects of lamivudine and tenofovir disoproxil fumarate tablets are:

- nausea
- rash
- diarrhea
- headache
- fatigue
- nasal signs and symptoms
- cough
- pain
- depression
- weakness

Lamivudine and Tenofovir Disoproxil Fumarate Tablets Co-packaged with Nevirapine Tablets may cause other serious side effects, including:

**Changes in body fat** can happen in some people who take antiviral medicines. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

**Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new symptoms after starting your HIV medicine.

The most common side effect of nevirapine, one component of lamivudine and tenofovir disoproxil fumarate tablets co-packaged with nevirapine tablets, is rash.

Tell your doctor if you have any side effects that bothers you or that does not go away while taking lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets.

These are not all the possible side effects of Lamivudine and Tenofovir Disoproxil Fumarate Tablets Co-packaged with Nevirapine Tablets. For more information ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may also report side effects to Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### **How Do I Store Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged with Nevirapine Tablets?**

- **Keep lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets and all other medicines out of reach of children.**
- Store lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets below 30°C (86°F).
- Keep lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets in its original container and keep the container tightly closed.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.

### **General Information about Lamivudine and Tenofovir Disoproxil Fumarate Tablets, co-packaged with Nevirapine Tablets:**

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets for a condition for which it was not prescribed. Do not give lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets to other people, even if they have the same symptoms you have. It may harm them.
- This Medication Guide summarizes the most important information about lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets that are written for health professionals.
- Do not use lamivudine and tenofovir disoproxil fumarate tablets, co-packaged with nevirapine tablets if the seal over bottle opening is broken or missing.

### **What are the Ingredients of Lamivudine and Tenofovir Disoproxil Fumarate Tablets, Co-packaged With Nevirapine tablets?**

#### **Lamivudine and Tenofovir Disoproxil Fumarate Tablets:**

Active Ingredients: lamivudine and tenofovir disoproxil fumarate.

Inactive Ingredients: colloidal silicon dioxide, croscarmellose sodium, FD&C Blue#2, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

**Nevirapine Tablets:**

Active Ingredient: Nevirapine.

Inactive Ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

All brands listed are the trademarks of their respective owners and are not trademarks of Aurobindo Pharma Limited.

**Rx only**

Manufactured for:

**Aurobindo Pharma USA, Inc.**

2400 Route 130 North

Dayton, NJ 08810

Manufactured by:

**Aurobindo Pharma Limited**

Unit-VII (SEZ)

Mahaboob Nagar (Dt)

AP-509302, INDIA

Issued: October 2013

Rx only

NDC 65862-755-03

**Lamivudine and Tenofovir  
Disoproxil Fumarate Tablets**

**300 mg/300 mg**

**Co-packaged with Nevirapine  
Tablets USP **200 mg****

1. BEND & TEAR 2. PEEL

Rx only

NDC 65862-755-03

**Lamivudine and Tenofovir  
Disoproxil Fumarate Tablets**

**300 mg/300 mg**

**Co-packaged with Nevirapine  
Tablets USP **200 mg****

1. BEND & TEAR 2. PEEL

EXP. :

B/N :



**Aurobindo Pharma Limited**  
Unit-VII (SEZ), Mahaboob Nagar (Dt)  
AP-509302, India  
M.L.No.: 22/MN/AP/2009/F/G

Take together

P0105541

1. BEND & TEAR 2. PEEL

EXP. :

B/N :



**Aurobindo Pharma Limited**  
Unit-VII (SEZ), Mahaboob Nagar (Dt)  
AP-509302, India  
M.L.No.: 22/MN/AP/2009/F/G

Take together

P0105541

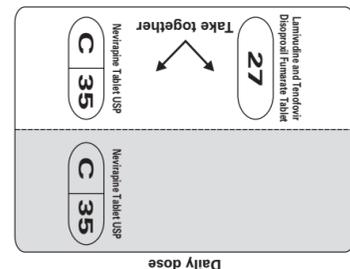
1. BEND & TEAR 2. PEEL



30 Day Supply Rx only

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg Co-packaged with Nevirapine Tablets USP 200 mg



NDC 65862-755-09

NDC 65862-755-09

Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg Co-packaged with Nevirapine Tablets USP 200 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only 30 Day Supply



Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 300 mg/300 mg: Each film-coated tablet contains 300 mg lamivudine USP and 300 mg tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

Nevirapine Tablets USP 200 mg: Each uncoated tablet contains 200 mg of nevirapine USP.

Usual Dosage: See package insert for Dosage and Administration.

Store below 30 °C (86 °F).

Keep this and all drugs out of the reach of children.

Carton contains 15 blister packs for a 30 day supply. Each blister pack contains two 1-day cards. Each 1-day card contains two nevirapine tablets USP 200 mg and one lamivudine and tenofovir disoproxil fumarate tablet 300 mg / 300 mg.

NDC 65862-755-09

Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg Co-packaged with Nevirapine Tablets USP 200 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only 30 Day Supply



Manufactured for: Aurobindo Pharma USA, Inc. 2400 Route 130 North Dayton, NJ 08810  
Manufactured by: Aurobindo Pharma Limited Unit-VII (SEZ), Mahaboob Nagar (Dt) AP-509302. India

Batch:

Expiry:



Place Pharmacy Label Here

P1010379

M.L.No.: 22/MN/AP/2009/F/G

Colours: P 348 C P Blue 072 C P 179 C P 3275 C Black

A/s : 148 x 132 x 107 mm