

## PRESCRIBING INFORMATION

### Lamivudine 150mg/Zidovudine 300 mg Tablets Co-Packaged With Nevirapine 200 mg Tablets

**Rx only**

#### WARNING

**Hematologic toxicity:** Zidovudine, one of the 2 active ingredients in Lamivudine Zidovudine fixed dose tablet, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease

**Myopathy:** Prolonged use of Zidovudine has been associated with symptomatic myopathy

**Lactic acidosis:** Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including Lamivudine, Zidovudine, and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur

**Exacerbations of hepatitis B:** Acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV -1 and have discontinued Lamivudine, which is one component of Lamivudine/ Zidovudine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Lamivudine Zidovudine and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted

**Hepatotoxicity:** Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with Nevirapine. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher CD4+ cell counts at initiation of therapy place patients at increased risk; women with CD4+ cell counts >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+ cell counts and at any time during treatment. 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

**Skin Reactions:** Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with Nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue 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

**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 severe hepatic, skin or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment.

## **1 INDICATION AND USAGE**

Lamivudine/Zidovudine co packed with Nevirapine tablets (150/300+200 mg) are indicated for the treatment of HIV-1 infection

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Adults:**

The recommended oral dose of Lamivudine/ Zidovudine tablets in HIV -I-infected adults and adolescents weighing greater than or equal to 30 kg is 1 tablet twice daily. The recommended dose for Nevirapine is one 200 mg tablet daily for the first 14 days, followed by one 200 mg tablet twice daily, in combination with other antiretroviral agents. The lead-in period has been observed to decrease the incidence of rash.

### **2.2 Pediatric patients:**

The recommended oral dosage of Lamivudine Zidovudine Tablets for pediatric patients who weigh greater than or equal to 30 kg is 1 tablet administered twice daily. The recommended oral dose for pediatric patients 15 days and older is  $150 \text{ mg/m}^2$  once daily for 14 days followed by  $150 \text{ mg/m}^2$  twice daily thereafter. The total daily dose should not exceed 400 mg for any patient. If the child is unable to swallow the tablets alternate formulations should be prescribed.

### **2.3 Patients requiring dosage adjustment**

Because Lamivudine/Zidovudine is a fixed dose combination tablet in Lamivudine Zidovudine co packed with Nevirapine tablets, it should not be prescribed if dosage adjustment is required.

## **3 DOSAGE FORMS AND STRENGTHS**

Lamivudine/ Zidovudine tablets are White to off white coloured oval shaped film coated tablet with "LZ" engraved on one side and break line on other side.

Nevirapine tablets are "white to off white oval shaped tablets with bisect on both sides.

## **3 CONTRAINDICATIONS**

Lamivudine Zidovudine co-packed with Nevirapine tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the

components of the product. Nevirapine is contraindicated in patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment

## **4 WARNINGS AND PRECAUTIONS**

### **5.1 Hemotologic Toxicity/Bone Marrow Suppression**

Zidovudine, a component of Lamivudine Zidovudine co packed with Nevirapine tablets, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV -1 disease. Lamivudine/Zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count less than 1,000 cells/mm<sup>3</sup> or hemoglobin less than 9.5 g/dL. Frequent blood counts are strongly recommended in patients with advanced HIV-1 disease who are treated with Lamivudine Zidovudine. Periodic blood counts are recommended for other HIV -I-infected patients. If anemia or neutropenia develops, dosage interruption may be needed.

### **5.2 Myopathy**

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

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

Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported nucleoside analogues alone or in combination, including Lamivudine, Zidovudine, with the use of and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering Lamivudine/ Zidovudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Lamivudine/ Zidovudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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

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

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

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

Lamivudine/ Zidovudine co packed with Nevirapine should not be administered concomitantly with other Lamivudine- or Zidovudine-containing products including EPIVIR<sup>®</sup> (Lamivudine) Tablets and Oral Solution, EPIVIR-HBV Tablets and Oral Solution, RETROVIR<sup>®</sup> (Zidovudine) Tablets, Capsules, Syrup, and iv Infusion, EPZICOM<sup>®</sup> (abacavir sulfate and Lamivudine) Tablets, or TRIZIVIR<sup>®</sup> (abacavir sulfate, Lamivudine, and Zidovudine) Tablets; or emtricitabine-containing products, including ATRIPLA<sup>®</sup> (efavirenz, emtricitabine, and tenofovir), EMTRIVA<sup>®</sup> (emtricitabine), or TRUVADA<sup>®</sup> (emtricitabine and tenofovir) or Viramune<sup>®</sup> (Nevirapine).

### **5.6 Pancreatitis**

Lamivudine/Zidovudine should be used with caution in patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis. Treatment with Lamivudine/ Zidovudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur

### **5.7 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.

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

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, Nevirapine should be permanently discontinued. 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 three-fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4<sup>+</sup> cell counts at initiation of Nevirapine therapy are at higher risk for symptomatic hepatic events with Nevirapine. 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, an unapproved use.

Increased Nevirapine trough concentrations have been observed in some patients with hepatic fibrosis or cirrhosis. Therefore, patients with either hepatic fibrosis or cirrhosis should be monitored carefully for evidence of drug-induced toxicity. Nevirapine should not be administered to patients with moderate or severe (Child-Pugh Class B or C)

## **5.8 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 1.5% of Nevirapine recipients compared to 0.1% 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. 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, transaminases should be measured immediately. Patients with rash-associated transaminase elevations should be permanently discontinued from Nevirapine.

Therapy with Nevirapine must be initiated with a 14-day lead-in period of 200 mg/day (150 mg/m<sup>2</sup>/day in pediatric patients), which has been shown to reduce the frequency of rash. Nevirapine should be discontinued if a patient experiences severe rash or any rash accompanied by constitutional findings. A patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg/day (150 mg/m<sup>2</sup>/day in pediatric patients) should not have their Nevirapine dose increased until the rash has resolved. The total duration of the once-daily lead-in dosing period should not exceed 28 days at which point an alternative regimen should be sought. Patients should 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.

### **5.9 Drug Interactions**

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and Zidovudine. Patients receiving interferon alfa with or without ribavirin and Lamivudine/ Zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of Lamivudine/Zidovudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh greater than 6)). Exacerbation of anemia has been reported in HIV -1/HCV co-infected patients receiving ribavirin and Zidovudine. Co-administration of ribavirin and Zidovudine is not advised.

See Table 6 and 7 for listings of established and potential drug interactions of Nevirapine. Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products and Nevirapine is not recommended. Co-administration of St. John's wort with non-nucleoside reverse transcriptase inhibitors (NNRTIs), including Nevirapine, is expected to substantially decrease NNRTI concentrations and may result in sub-optimal levels of Nevirapine and lead to loss of virologic response and possible resistance to Nevirapine or to the class of NNRTIs. Co administration of Nevirapine and Efavirenz is not recommended as this combination has been associated with an increase in adverse reactions and no improvement in efficacy.

### **5.10 Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including Lamivudine/Zidovudine or Nevirapine. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond

may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

### 5.11 Fat Redistribution

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

## 6. ADVERSE REACTIONS:

### 6.1 Clinical Trials Experience

No clinical studies have been conducted using Lamivudine Zidovudine co packed with Nevirapine tablets

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

Lamivudine Plus Zidovudine Administered As Separate Formulations: In 4 randomized, controlled trials of Lamivudine 300 mg per day plus Zidovudine 600 mg per day, the following selected adverse reactions and laboratory abnormalities were observed (See Table 1)

**Table 1: Selected Clinical Adverse Reactions (≥5% Frequency) in 4 Controlled Clinical Trials with EPIVIR 300 mg/day and Zidovudine 600 mg/day**

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

<b>Respiratory</b>	
Nasal signs & symptoms	20%
Cough	18%
<b>Skin</b>	
Skin rashes	9%
<b>Musculoskeletal</b>	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received Lamivudine in of controlled clinical trials.

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

**Table 2: Frequencies of Selected Laboratory Abnormalities Among Adults in 4 Controlled Clinical Trials of EPIVIR 300 mg/day plus RETROVIR 600 mg/day\***

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

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

n = Number of patients assessed.

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

## **Nevirapine**

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

related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving Nevirapine in placebo-controlled trials are shown in the following table3.

**Table 3 Percentage of Patients 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	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0
Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2.0	0.5
Abdominal pain	0.1	0.4	2.0	0
Myalgia	0.2	0	1.2	2.0

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

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

*Laboratory Abnormalities*

Liver enzyme test abnormalities (AST, ALT) were observed more frequently in patients receiving Nevirapine than in controls. 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, and thrombocytopenia) were observed with similar frequencies in clinical trials comparing Nevirapine and control regimens.

**Table 5 Percentage of Adult Patients 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	5.3	4.4	14.0	4.0
SGOT (AST) >250 U/L	3.7	2.5	7.6	1.5
Bilirubin >2.5 mg/dL	1.7	2.2	1.7	1.5
<b>Hematology</b>				
Hemoglobin <8.0 g/dL	3.2	4.1	0	0
Platelets <50,000/mm <sup>3</sup>	1.3	1.0	0.4	1.5
Neutrophils <750/mm <sup>3</sup>	13.3	13.5	3.6	1.0

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

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

## **6.2 Post marketing experience:**

In addition to adverse reactions reported from clinical trials, the following reactions have been identified during post-approval use Lamivudine/Zidovudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Body as a Whole: Redistribution/accumulation of body fat

Cardiovascular: Cardiomyopathy.

Endocrine and Metabolic: Gynecomastia, hyperglycemia.

Gastrointestinal: Oral mucosal pigmentation, stomatitis.

General: Vasculitis, weakness.

Hemic and Lymphatic: Anemia, (including pure red cell aplasia and anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, post treatment exacerbation of hepatitis B

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.  
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

**Nevirapine:** In addition to the adverse events identified during clinical trials, the following adverse reactions have been identified during post-approval use of Nevirapine.

Body as a Whole: fever, somnolence, drug withdrawal, redistribution/accumulation of body fat.

Gastrointestinal: vomiting

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

Hematology: Anemia, eosinophilia, neutropenia

Musculoskeletal: arthralgia, rhabdomyolysis associated with skin and/or liver reactions

Neurologic: paraesthesia

Skin and Appendages: allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities plus

one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of Nevirapine.

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

## **7 DRUG INTERACTIONS**

No drug interaction studies have been conducted using Lamivudine Zidovudine co packed with Nevirapine tablets

### Antiretroviral Agents

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

Zidovudine-Stavudine: Concomitant use of Lamivudine Zidovudine with stavudine should be avoided since an antagonistic relationship with Zidovudine has been demonstrated in vitro.

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

### Doxorubicin

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

### Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

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

### Interferon- and Ribavirin-Based Regimens

Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was Co administered with Lamivudine in HIV1/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

### Trimethoprim / Sulfamethoxazole (TMP/SMX)

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

### **Nevirapine:**

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A and 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs

that are metabolized by these enzyme systems may have lower than expected plasma levels when co-administered with Nevirapine.

In addition to established drug interactions, there may be potential pharmacokinetic interactions between Nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are also listed in Table 7.

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

**Table 6 Established and Potential Drug Interactions: Use With Caution, Alteration in Dose or Regimen May Be Needed Due to Drug Interaction Established Drug Interactions:**

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
Atazanavir/Ritonavir	↓ Atazanavir ↑ Nevirapine	Do not co-administer Nevirapine with atazanavir because Nevirapine substantially decreases atazanavir exposure.
Clarithromycin	↓ Clarithromycin ↑14-OH clarithromycin	Clarithromycin exposure was significantly decreased by Nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against Mycobacterium avium-intracellulare complex, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Efavirenz	↓ Efavirenz	There has been no determination of appropriate doses for the safe and effective use of this combination
Ethinyl estradiol and Norethindrone	↓Ethinyl estradiol ↓ Norethindrone	Oral contraceptives and other hormonal methods of birth control should not be used as

		the sole method of contraception in women taking Nevirapine, since Nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.
Fluconazole	↑Nevirapine	Because of the risk of increased exposure to Nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for Nevirapine-associated adverse events
Fosamprenavir	↓Amprenavir ↑Nevirapine	Co-administration of Nevirapine and fosamprenavir without ritonavir is not recommended.
Fosamprenavir/Ritonavir	↓Amprenavir ↑Nevirapine	No dosing adjustments are required when Nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir twice daily.
Indinavir	↓ Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/Ritonavir	↓Lopinavir	Lopinavir/ritonavir 400/100 mg tablets can be used twice daily in combination with Nevirapine with no dose adjustment in antiretroviral-

		<p>naïve patients.</p> <p>A dose increase of lopinavir/ritonavir tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with Nevirapine in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence).</p> <p>A dose increase of lopinavir/ritonavir oral solution to 533/133 mg twice daily with food is recommended in combination with Nevirapine.</p> <p>In children 6 months to 12 years of age, consideration should be given to increasing the dose of lopinavir/ritonavir to 13/3.25 mg/kg for those 7 to &lt;15 kg; 11/2.75 mg/kg for those 15 to 45 kg; and up to a maximum dose of 533/133 mg for those &gt;45 kg twice daily when used in combination with Nevirapine, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected</p>
Methadone	↓ Methadone	<p>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.</p>
Nelfinavir	↓Nelfinavir M8 Metabolite	<p>The appropriate dose for</p>

	↓Nelfinavir Cmin	nelfinavir in combination with Nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in Nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a Nevirapine-containing regimen may use rifabutin instead.
Saquinavir/ritonavir	The interaction between Nevirapine and saquinavir/ritonavir has not been evaluated	The appropriate doses of the combination of Nevirapine and saquinavir/ritonavir with respect to safety and efficacy have not been established.

**Table: 7 Potential Drug Interactions:**

<b>Drug Class</b>	<b>Examples of Drugs</b>	
Antiarrhythmics	Amiodarone, disopyramide, lidocaine	Plasma concentrations may be decreased.
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide	Plasma concentrations may be decreased
Antifungals	Itraconazole	Plasma concentrations of some

		azole antifungals may be decreased. Nevirapine and itraconazole should not be administered concomitantly due to a potential decrease in itraconazole plasma concentrations.
Calcium channel blockers	Diltiazem, nifedipine, verapamil	Plasma concentrations may be decreased.
Cancer chemotherapy	Cyclophosphamide	Plasma concentrations may be decreased.
Ergot alkaloids	Ergotamine	Plasma concentrations may be decreased.
Immunosuppressants	Cyclosporin, tacrolimus, sirolimus	Plasma concentrations may be decreased.
Motility agents	Cisapride	Plasma concentrations may be decreased.
Opiate agonists	Fentanyl	Plasma concentrations may be decreased.
Antithrombotics	Warfarin	Plasma concentrations may be increased. Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

## 8. USE IN SPECIFIC POPULATIONS

### 8.1 P Pregnancy Category C-Lamivudine and Zidovudine.

**Fetal Risk Summary:** There are no adequate and well-controlled studies of Lamivudine and Zidovudine in pregnant women. Clinical trial data demonstrate that maternal Zidovudine treatment during pregnancy reduces vertical transmission of HIV -1 infection to the fetus. Lamivudine and Zidovudine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Clinical Considerations:** Treatment of HIV during pregnancy optimizes the health of both mother and fetus. Clinical trial data reviewed by FDA demonstrate that maternal Zidovudine treatment significantly reduces vertical transmission of HI V-I infection to the fetus. Published data suggest that combination antiretroviral regimens may reduce the rate of vertical transmission even further. Pharmacokinetics of Lamivudine and Zidovudine in pregnant women is similar to the pharmacokinetics in non pregnant women. No dose adjustments are needed during pregnancy.

In a clinical trial, adverse events among HIV -I-infected women were not different among untreated women and women treated with Zidovudine. It is not known whether risks of adverse events associated with Lamivudine are altered in pregnant women compared with other HIV-1-infected patients

**Lamivudine:** Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies conducted in South Africa. The study assessed pharmacokinetics in: 16 women at 36 weeks gestation using 150 mg Lamivudine twice daily with Zidovudine, 10 women at 38 weeks gestation using 150 mg Lamivudine twice daily with Zidovudine,

and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. Lamivudine pharmacokinetics in pregnant women was similar to those seen in non pregnant adults and in post partum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

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

Zidovudine pharmacokinetics was studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation.

The pharmacokinetics of Zidovudine was similar to that of non pregnant adults. Consistent with passive transmission of the drug across the placenta, Zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.

**Nevirapine:** Teratogenic Effects, Pregnancy Category B.

The Antiretroviral Pregnancy Registry, which has been surveying pregnancy outcomes since January 1989, has not found an increased risk of birth defects following first trimester exposures to Nevirapine. The prevalence of birth defects after any trimester exposure to Nevirapine is comparable to the prevalence observed in the general population. Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic Nevirapine therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with CD4+ cell counts >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. Nevirapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to Lamivudine, Zidovudine and Nevirapine and other antiretrovirals an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

### **8.3 Nursing Mothers**

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

#### **8.4 Pediatric Use**

The safety, pharmacokinetic profile, and virologic and immunologic responses of Nevirapine and Lamivudine have been evaluated in HIV-1 infected pediatric patients' age 3 months to 18 years. Lamivudine Zidovudine combination tablet should not be administered to pediatric patients weighing less than 30 kg, because it is a fixed-dose combination that cannot be adjusted for this patient population.

#### **8.5 Geriatric Use**

Individual Clinical studies of Lamivudine Zidovudine and Nevirapine did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Alternate formulations are recommended if dose adjustment is necessary

#### **8.6 Renal impairment**

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

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of Nevirapine. Nevirapine is extensively metabolized by the liver and Nevirapine metabolites are extensively eliminated by the kidney. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known. No adjustment in Nevirapine dosing is required in patients with CrCL  $\geq$ 20 mL/min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated

#### **8.7 Hepatic impairment**

A reduction in the daily dose of Zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Lamivudine Zidovudine is not recommended for patients with impaired hepatic function because it is a fixed-dose combination that cannot be adjusted.

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

### **10 OVERDOSAGE**

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

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

Zidovudine: Acute overdoses of Zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, confusion, and 1 report of a grandmal seizure. Hematologic changes were transient. All patients recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of Zidovudine, while elimination of its primary metabolite, 3'-azido-3'-deoxy-5'-O-β-D3glucopyranuronosylthymidine (GZDV), is enhanced.

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

## 11. DESCRIPTION

Lamivudine Zidovudine co packed with Nevirapine (40/150+200mg) tablets are for oral administration

### **Lamivudine:**

Lamivudine (also known as 3TC) is a synthetic nucleoside analogue with activity against HIV-1 and HBV. 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 di deoxy analogue of cytidine. Lamivudine has, also been referred to as (-)-2',3'-di deoxy, 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. Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

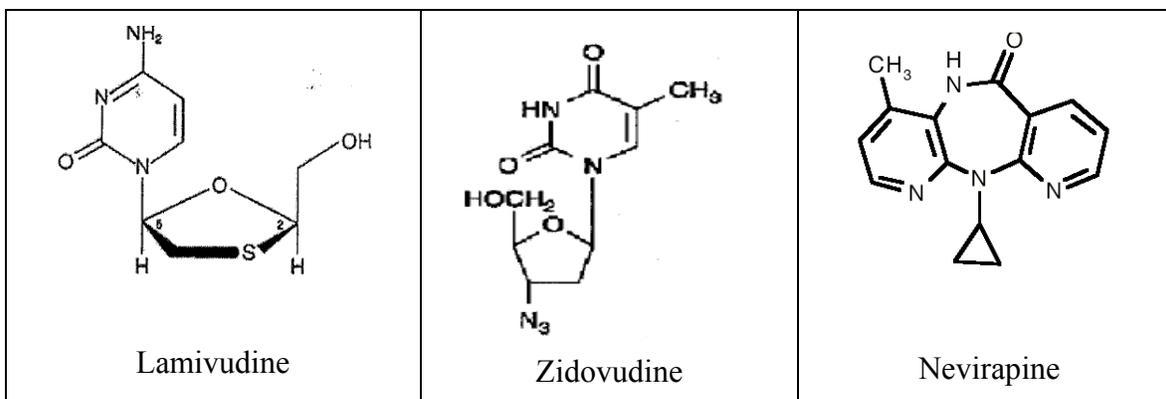
### **Zidovudine**

The chemical name of Zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub> and a molecular weight of 267.24. Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/mL 367 in water at 25°C.

### **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 dipyrindodiazepinone chemical class of compounds.

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



## 12. CLINICAL PHARMACOLOGY

### 12.1 Mechanism of action

Lamivudine, Zidovudine and Nevirapine are antiviral agents (See clinical pharmacology 12.4)

### 12.3 Pharmacokinetics

Lamivudine Zidovudine 150/300 mg and Nevirapine 200 mg tablet was bioequivalent to one combivir<sup>®</sup> tablet and Viramune<sup>®</sup> tablet respectively following single-dose administration to fasting healthy subjects

**Lamivudine:** The pharmacokinetic properties of Lamivudine in fasting patients are summarized in Table 8. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of Lamivudine is recovered as unchanged drug in the urine. Metabolism of Lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

**Zidovudine:** The pharmacokinetic properties of Zidovudine in fasting patients are summarized in Table 8. Following oral administration, Zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolisms. The major metabolite of Zidovudine is GZDV. GZDV area under the curve (AUC) is about 3-fold greater than the Zidovudine AUC. Urinary recovery of Zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the Zidovudine AUC.

**Table 8. Pharmacokinetic parameters\* for Lamivudine and Zidovudine in adults**

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

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

<sup>^</sup>Median, \*\*children, <sup>§</sup> adults, <sup>^^</sup> approximate range

### **Nevirapine:**

Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9% (mean ± SD) for a 50 mg tablet. Peak plasma Nevirapine concentrations of 2 ± 0.4 µg/mL (7.5 µM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, Nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady-state trough Nevirapine concentrations of 4.5 ± 1.9 µg/mL (17 ± 7 µM), (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.

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 ± 0.09 L/kg, suggesting that Nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is also found in breast. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 µg/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% (±5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

*In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that Nevirapine is extensively bio transformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of Nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A and CYP2B6 families, although

other isozymes may have a secondary role. In a mass balance/excretion study 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 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of Nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

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

#### **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  $\gamma$ .

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

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

**Lamivudine:** The antiviral activity of Lamivudine against HIV -1 was assessed in a Number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC<sub>50</sub> values (50% effective

concentrations) were in the range of 0.003 to 15  $\mu\text{M}$  ( $1 \mu\text{M} = 0.23 \text{ mcg/mL}$ ). HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median  $\text{EC}_{50}$  values of 0.429  $\mu\text{M}$  (range: 0.200 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  $\text{EC}_{50}$  values of Lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120  $\mu\text{M}$ , and against HIV-2 isolates from 0.003 to 0.120  $\mu\text{M}$  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.

**Zidovudine:** The antiviral activity of Zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The  $\text{EC}_{50}$  and  $\text{EC}_{90}$  values for Zidovudine were 0.01 to 0.49  $\mu\text{M}$  ( $1 \mu\text{M} = 0.27 \text{ mcg/mL}$ ) and 0.1 to 9  $\mu\text{M}$ , respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median  $\text{EC}_{50}$  values 0.011  $\mu\text{M}$  (range: 0.005 to 0.110  $\mu\text{M}$ ) from Virco ( $n = 92$  baseline samples from COLA40263) and 0.0017  $\mu\text{M}$  (0.006 to 0.0340  $\mu\text{M}$ ) from Monogram Biosciences ( $n = 135$  baseline samples from ESS30009). The  $\text{EC}_{50}$  values of Zidovudine against different HIV-1 clades (A~G) ranged from 0.00018 to 0.02  $\mu\text{M}$ , and against HIV-2 isolates from 0.00049 to 0.004  $\mu\text{M}$ . In cell culture drug combination studies, Zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) Abacavir, Didanosine, Lamivudine, and zalcitabine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and Nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, Ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of Zidovudine in cell culture.

**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  $\text{EC}_{50}$  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  $\text{EC}_{50}$  value was 470 nM in this study. The median  $\text{EC}_{50}$  value was 63 nM (range 14-302 nM,  $n=29$ ) against clinical isolates of HIV-1 clades A, B, C, D, F, G, and H, and circulating recombinant forms CRF01\_AE, CRF02\_AG and CRF12\_BF. Nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates ( $n=3$ ) or HIV-2 isolates ( $n=3$ ) replicating in cord blood mononuclear cells. Nevirapine in combination with efavirenz exhibited strong antagonistic anti-HIV-1 activity in cell culture and was additive to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor enfuvirtide. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, Lamivudine, stavudine, tenofovir and Zidovudine. The anti-HIV-1 activity of Nevirapine was antagonized by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin in cell culture

### **Resistance:**

**Lamivudine Plus Zidovudine Administered As Separate Formulations:** In patients receiving Lamivudine monotherapy or combination therapy with Lamivudine plus

Zidovudine, HIV -1 isolates from most patients became phenotypically and genotypically resistant to Lamivudine within 12 weeks. In some patients harboring Zidovudine-resistant virus at baseline, phenotypic sensitivity to Zidovudine was restored by 12 weeks of treatment with Lamivudine and Zidovudine. Combination therapy with Lamivudine plus Zidovudine delayed the emergence of amino acid substitutions conferring resistance to Zidovudine.

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

Lamivudine: Lamivudine-resistant isolates of HIV-1 have been selected in cell culture and have also been recovered from patients treated with Lamivudine or Lamivudine plus Zidovudine. Genotypic analysis of isolates selected in cell culture and recovered from

Lamivudine-treated patients showed that the resistance was due to a specific amino acid substitution in the HIV -1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V II).

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

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

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

Genotypic analysis of isolates from antiretroviral-naïve patients experiencing virologic failure (n=71) receiving Nevirapine once daily (n=25) or twice daily (n=46) in combination with Lamivudine and stavudine (study 2NN) for 48 weeks showed that

isolates from 8/25 and 23/46 patients, respectively, contained one or more of the following NNRTI resistance-associated substitutions: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

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

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

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

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

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, mutagenesis, impairment of fertility**

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

**Impairment of Fertility:**

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

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

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

#### Impairment of Fertility:

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

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

## 14 CLINICAL STUDIES

There have been no clinical trials conducted with Lamivudine Zidovudine co packed with Nevirapine tablets. Lamivudine Zidovudine tablets and Nevirapine tablets were bioequivalent to Combivir<sup>®</sup> tablets and Viramune<sup>®</sup> tablets when administered under fasting conditions in healthy subjects.

### 14.1 clinical studies in adults

Lamivudine Plus Zidovudine: The NUCB3007 (CAESAR) study was conducted using Lamivudine 150-mg Tablets (150 mg twice daily) and Zidovudine 100-mg Capsules (2 x 100 mg 3 times daily). CAESAR was a multi-center, double-blind, placebo-controlled study comparing continued current therapy (Zidovudine alone (62% of patients) or Zidovudine with didanosine or zalcitabine (38% of patients)) to the addition of

Lamivudine or Lamivudine plus an investigational non nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1,816 HIV-1-infected adults with 25 to 250 (median 122) CD4 cells/mm<sup>3</sup> at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on study was 12 months. Results are summarized in Table 9.

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

<b>Endpoint</b>	<b>Current Therapy (n = 460)</b>	<b>EPIVIR plus Current Therapy (n = 896)</b>	<b>EPIVIR plus a NNRTI* plus Current Therapy (n = 460)</b>
HIV -1 progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

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

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

The utility of Zidovudine alone for the prevention of maternal-fetal HIV-1 transmission was demonstrated in a randomized, double-blind, placebo-controlled trial conducted in HIV-1-infected pregnant women with CD4+ cell counts of 200 to 1,818 cells/in<sup>3</sup> (median in 614 the treated group: 560 cells/in<sup>3</sup>) who had little or no previous exposure to Zidovudine. Oral zidovudine was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by iv administration of Zidovudine during labor and delivery. Following birth, neonates received oral Zidovudine syrup for 6 weeks. The study showed a statistically significant difference in the incidence of HIV-1 infection in the neonates (based on viral culture from peripheral blood) between the group receiving Zidovudine and the group receiving placebo. Of 363 neonates evaluated in the study, the estimated risk of HIV-1 infection was 7.8% in the group receiving Zidovudine and 24.9% in the placebo group, a relative reduction in transmission risk of 68.7%. Zidovudine was well tolerated by mothers and infants. There was no difference in pregnancy-related adverse events between the treatment groups.

## Nevirapine:

Trial BI 1090 was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1 infected patients with  $<200$  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 patients. 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 patients (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%). The patients (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 study. Prior to unblinding the trial, the primary endpoint was changed to proportion of patients with HIV-1 RNA  $<50$  copies/mL and not previously failed at 48 weeks. Treatment response and outcomes are shown in Table 10.

**Table 10: BI 1090 Outcomes through 48 Weeks**

<b>Outcome</b>	<b>VIRAMUNE (N=1121) %</b>	<b>Placebo (N=1128) %</b>
Responders at 48 weeks: HIV-1 RNA $<50$ copies/mL	18.0	1.6
Treatment Failure	82.0	98.4
Never suppressed viral load	44.6	66.4
Virologic failure after response	7.2	4.3
CDC category C event or death	9.6	11.2
Added antiretroviral therapy <sup>1</sup> while $<50$ copies/mL	5.0	0.9
Discontinued trial therapy due to AE	7.0	5.9
Discontinued trial $<48$ weeks <sup>2</sup>	8.5	9.8

<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 study population (64 cells/mm<sup>3</sup> vs 22 cells/mm<sup>3</sup>, respectively), as well as for patients 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 study, 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 patients with CD4<sup>+</sup> cell counts of 200-600 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 patients had mean baseline HIV-1 RNA of 4.41 log<sub>10</sub> copies/mL (25,704 copies/mL) and mean baseline CD4+ cell count of 376 cells/mm<sup>3</sup>. The primary endpoint was the proportion of patients with HIV-1 RNA <400 copies/mL and not previously failed at 48 weeks. The virologic responder rates at 48 weeks were 45% for patients treated with Nevirapine +Zidovudine + didanosine, 19% for patients treated with Zidovudine + didanosine, and 0% for patients treated with Nevirapine +Zidovudine.

CD4+ 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 87cells/mm<sup>3</sup> in the ZDV+ddI patients. The Nevirapine +ZDV group mean decreased by 6 cells/mm<sup>3</sup> below baseline.

#### **14.2 clinical studies in pediatrics:**

No clinical studies were done in pediatric patients with Lamivudine Zidovudine co-packed with Nevirapine tablets

### **16 HOW SUPPLIED/STORAGE AND HANDLING**

Lamivudine /Zidovudine tablets are White to off white coloured oval shaped film coated tablets with “LZ” engraved on one side and break line on other side.

Lamivudine /Zidovudine tablets are supplied in bottles of 60 tablets.

Nevirapine tablets are "white to off white oval shaped tablets with bisect on both sides.

Nevirapine tablets are supplied in bottles of 60 tablets.

Dispense in tight container as defined in the USP/NF.

### **STORAGE**

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

### **17. PATIENT COUNSELLING INFORMATION**

See medication guide

*See MEDICATION GUIDE*

The Medication Guide provides written information for the patient, and should be dispensed with each new prescription and refill. A medication guide is supplied as a tear-off following the full prescribing information.

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

Neutropenia and Anemia: Patients should be informed that the important toxicities associated with Zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV-1 disease

Hepatotoxicity and Skin Reactions: Patients should be informed of the possibility of severe liver disease or skin reactions associated with Lamivudine Zidovudine co packed

with Nevirapine that may result in death. Patients developing signs or symptoms of liver disease or severe skin reactions should be instructed to discontinue Lamivudine zidovudine co packed with Nevirapine tablets as this consists of Nevirapine and seek medical attention immediately, including performance of laboratory monitoring

Patients should be informed of the importance of early recognition of symptoms of symptomatic hyperlactatemia or lactic acidosis syndrome, which include unexplained weight loss, abdominal discomfort, nausea; vomiting, fatigue, dyspnea, and motor weakness (see Warnings and Precautions).

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

Drug Interactions: Patients should be cautioned about the use of other medications, including ganciclovir, interferon alfa, and ribavirin, which may exacerbate the toxicity of Zidovudine (see Drug Interactions) Nevirapine may decrease the plasma concentrations of methadone by increasing its hepatic metabolism. Methadone-maintained patients beginning Nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Hormonal methods of birth control, other than depomedroxy-progesterone acetate (DMPA), should not be used as the sole method of contraception in women taking Lamivudine/ Zidovudine co packed with Nevirapine tablets since Nevirapine may lower the plasma levels of these medications

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

Information About Therapy with Lamivudine/Zidovudine co packed with Nevirapine tablets:

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

Lamivudine/Zidovudine co packed with Nevirapine tablet is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV -1 infection, including opportunistic infections. Patients should be advised that the use of Lamivudine/Zidovudine co packed with Nevirapine tablet has not been shown to reduce the risk of transmission of HIV -1 to others through sexual contact or blood contamination. Patients should be advised of the importance of taking Lamivudine/Zidovudine co packed with Nevirapine tablet exactly as it is prescribed.

Lamivudine/Zidovudine co packed with Nevirapine tablet should not be coadministered with drugs containing Lamivudine, Zidovudine, or emtricitabine, including EPIVIR

(Lamivudine), EPVIR-HBV (Lamivudine), RETROVIR (Zidovudine), EPZICOM (abacavir sulfate and Lamivudine), TRIZIVIR (abacavir sulfate, lamivudine, and Zidovudine), ATRIPLA (efavirenz, emtricitabine, and tenofovir), EMTRIVA (emtricitabine), or TRUVADA (emtricitabine and tenofovir) or VIRAMUNE (Nevirapine) (see Warnings and Precautions ).

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

## **MEDICATION GUIDE**

### **Lamivudine (150 mg)/Zidovudine (300 mg) Tablets Co-Packaged with Nevirapine (200 mg) Tablets**

**Generic name:** Lamivudine/Zidovudine (lah MIH vue deen and zye DOE vue deen) tablets co-packaged with Nevirapine (na VAIR a peen) tablets.

Read this Medication Guide before you start taking the combination of Lamivudine/ Zidovudine co-packaged with Nevirapine tablets, and each time you get a refill because there may be new information. This information does not take the place of talking with your doctor. You and your doctor should discuss regarding these medicines when you start taking it and at regular checkups. You should stay under a doctor's care while using these medications. You should consult with your doctor before making any changes to your medications, except in any of the special circumstances described below regarding rash or liver problems.

#### **What is the most important information I should know about the Lamivudine/Zidovudine tablets co-packaged with Nevirapine tablets.?**

Patients taking the Lamivudine/ Zidovudine tablets may develop:

##### **Lactic Acidosis**

Lactic acidosis and severe liver problems, including fatal cases, have been reported with the use of Lamivudine and Zidovudine, alone or in combination. Contact your doctor immediately if you experience nausea, vomiting, or unusual or unexpected stomach discomfort; weakness and tiredness; shortness of breath; weakness in the arms and legs; yellowing of the skin or eyes; or pain in the upper stomach area. These may be early symptoms of lactic acidosis or liver problems.

##### **Worsening of hepatitis B virus (HBV) infection**

Patients with HBV infection, who take Lamivudine /Zidovudine tablets and then stop them, may get “flare-ups” of their hepatitis. “Flare-up” is when the disease suddenly returns in a worse way than before. If you have HBV infection, your doctor should closely monitor your liver function for several months after stopping Lamivudine /Zidovudine tablets. You may need to take anti-HBV medicines.

### **Hematologic toxicity**

Lamivudine/Zidovudine tablets have been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV disease. Serious blood problems including low levels of red and/or white blood cells have occurred with the use of Zidovudine. Contact your doctor immediately if you develop unusual fatigue, pale skin, sore throat, fever, or chills which may be signs of blood problems.

Prolonged use of Lamivudine /Zidovudine tablets has been associated with symptomatic myopathy.

Patients taking the co-packaged Nevirapine tablets may develop:

Severe liver disease or skin reactions that can lead to death sometimes. The risk of these reactions is greatest during the first 18 weeks of treatment, but these reactions also can occur later.

### **Liver Reactions**

**Any patient can experience liver problems while taking Nevirapine. However, women and patients who have higher CD4 counts when they begin treatment with Nevirapine have a greater chance of developing liver damage. Women with CD4 counts higher than 250 cells/mm<sup>3</sup> are at the greatest risk of these events. If you are a woman with CD4>250 cells/mm<sup>3</sup> or a man with CD4>400 cells/mm<sup>3</sup> you should not begin taking Nevirapine unless you and your doctor have decided that the benefit of doing so outweighs the risk. Liver problems are often accompanied by a rash.**

Patients starting with abnormal liver function tests and patients suffering from hepatitis B or C have a greater chance of developing further increases in liver function tests after starting Nevirapine and throughout therapy.

**In rare cases liver problems have led to liver failure and can lead to a liver transplant or death. Therefore, if you develop any of the following symptoms of liver problems stop taking and call your doctor right away:**

- general ill feeling or “flu-like” symptoms

- dark urine (tea colored)
- tiredness
- pale stools (bowel movements)
- nausea (feeling sick to your stomach)
- pain, ache, or sensitivity to touch on your right side below your ribs
- lack of appetite
- yellowing of your skin or whites of your eyes

Your doctor should check you and do blood tests often to check your liver function during the first 18 weeks of therapy. Checks for liver problems should continue regularly during treatment period.

### **Skin Reactions**

Skin rash is the most common side effect of Nevirapine. Most rashes occur in the first 6 weeks of treatment. In a small number of patients, **rash can be serious and result in death.** Therefore **if you develop a rash with any of the following symptoms stop using Nevirapine and call your doctor immediately:**

- general ill feeling or “flu-like” symptoms
- blisters
- fever
- mouth sores
- muscle or joint aches
- swelling of your face
- conjunctivitis (red or inflamed eyes, like “pink eye) • tiredness
- any of the symptoms of liver problems discussed above

**If your doctor tells you to stop treatment with Nevirapine because you have experienced the serious liver or skin reactions described above, never take Nevirapine again.**

**These are not all the side effects of Lamivudine, Zidovudine and Nevirapine. (See the section "What are the possible side effects?" for more information.) Inform your doctor if you have any side effects from these medications.**

**What is the Lamivudine/ Zidovudine tablets co-packaged with Nevirapine tablets?**

Lamivudine and Zidovudine with Nevirapine are antiviral medications. They are in a category of HIV medicines called reverse transcriptase inhibitors. Lamivudine and Zidovudine inhibit the reproduction of HIV in the body.

Lamivudine and Zidovudine are used together to treat the human immunodeficiency virus (HIV), which causes the acquired immunodeficiency syndrome (AIDS). Lamivudine and Zidovudine is not a cure for HIV or AIDS.

Lamivudine and Zidovudine may also be used for purposes other than those listed in this medication guide.

**Who should not take Lamivudine /Zidovudine Tablets along with Nevirapine Tablets?**

- Do not take if you are allergic to Lamivudine, Zidovudine or Nevirapine or any of its ingredients. Your doctor or pharmacist can tell you about the inactive ingredients.
- Do not restart the medication after you recover from side effects of these medications such as serious blood problems, lactic acidosis, serious liver or skin reactions that happened when you took these medications without the advice of your doctor.
- Do not take these medications if you take certain medicines. (See “Can I take other medicines?” for a list of medicines.)
- Do not take these medications if you are not infected with HIV.

**What should I tell my doctor before taking these medications?**

Before taking the Lamivudine /Zidovudine tablets co-packaged with Nevirapine, tell your doctor if you

- Have kidney disease or are undergoing dialysis;
- Have liver disease or have had hepatitis;
- Have bone marrow suppression;

- Have skin conditions, such as a rash
- Are pregnant, planning to become pregnant, or are breast feeding

### **How should I take these medications?**

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

- Take each dose with a full glass of water.
- These medications are taken without food.
- The usual dose of the Lamivudine /Zidovudine tablets (both the medications are present in one single tablet) for adult is 1 tablet taken twice 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. Starting with one dose a day 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.
- Do not let your Lamivudine /Zidovudine tablets or Nevirapine tablets run out.
- If you stop taking Nevirapine tablets for more than 7 days, ask your doctor before you start taking them again.
- 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.
- Store these medications at room temperature away from moisture and heat.

### **What happens if I miss a dose?**

- Do not miss a dose. If you forget then, take the missed dose as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and take only the

next regularly scheduled dose. **Do not** take a double dose of this medication unless your doctor directs otherwise.

- If you miss too many doses, then contact your doctor.

### **What happens if I overdose?**

- If you suspect that you have taken too much of these medications, contact your local poison control center or emergency room right away.
- Symptoms of a Lamivudine and Zidovudine overdose may include nausea, vomiting, headache, dizziness, drowsiness, lethargy, confusion, and seizures.

### **Can I take other medicines with Lamivudine /Zidovudine tablets and Nevirapine tablets ?**

Other medications may interact with these medications resulting in decreased effectiveness and/or side effects. Talk to your doctor and pharmacist before taking any other prescription or over-the-counter medicines, including vitamins, minerals, and herbal products, during treatment.

- Lamivudine/ Zidovudine co packed with Nevirapine should not be administered concomitantly with other Lamivudine- or Zidovudine-containing products including EPIVIR<sup>®</sup> (Lamivudine) Tablets and Oral Solution, EPIVIR-HBV Tablets and Oral Solution, RETROVIR<sup>®</sup> (Zidovudine) Tablets, Capsules, Syrup, and iv Infusion, EPZICOM<sup>®</sup> (Abacavir sulfate and lamivudine) Tablets, or TRIZIVIR<sup>®</sup> (Abacavir sulfate, Lamivudine, and Zidovudine) Tablets; or emtricitabine-containing products, including ATRIPLA<sup>®</sup> (Efavirenz, emtricitabine, and Tenofovir), EMTRIVA<sup>®</sup> (emtricitabine), or TRUVADA<sup>®</sup> (emtricitabine and Tenofovir) or Viramune<sup>®</sup> (Nevirapine).
- Do not take Nizoral<sup>®</sup> (ketoconazole) or Rifadin<sup>®</sup>/Rifamate<sup>®</sup>/Rifater<sup>®</sup> (rifampin), atazanavir with Nevirapine.
- Tell your doctor if you take Biaxin<sup>®</sup> (clarithromycin), Diflucan<sup>®</sup> (fluconazole), methadone, or Mycobutin<sup>®</sup> (rifabutin). Nevirapine may not be right for you, or you may need careful monitoring.

- It is recommended that you do not take products containing St. John's wort, which can reduce the amount of Nevirapine in your body.
- If you take birth control pills, you should not rely on them to prevent pregnancy. They may not work if you take Nevirapine. Talk with your doctor about other types of birth control that you can use.

### **What should I avoid while taking these medications?**

- Follow your doctor's instructions with respect to high-risk activities such as unprotected sex and personal items that can have blood or body fluids on them, like toothbrushes razor, blades and needles. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood. These medications do not cure HIV or AIDS and you can still transmit the virus to others during therapy with this medication.
- The Centers for Disease Control and Prevention advises mothers with HIV not to breast feed so they will not pass HIV to the infant through their milk. Ask your doctor about the best way to feed your infant.
- Avoid alcohol. Alcohol may increase the risk of damage to the pancreas and/or liver.

### **What are the possible side effects?**

(Also see "**What is the most important information I should know about Lamivudine/ Zidovudine tablets co-packaged with Nevirapine tablets?**" at the beginning of this Medication Guide.)

#### **Lamivudine/Zidovudine tablet can cause**

- Serious blood problems including low levels of red and/or white blood cells have occurred with the use of Zidovudine. Contact your doctor immediately if you develop unusual fatigue, pale skin, sore throat, fever, or chills which may be signs of blood problems.
- Lactic acidosis and severe liver problems, including fatal cases, have been reported with the use of reverse transcriptase inhibitors, such as Zidovudine and Lamivudine, alone or in combination. Contact your doctor immediately if you experience nausea, vomiting, or unusual or unexpected stomach discomfort; weakness and tiredness;

shortness of breath; weakness in the arms and legs; yellowing of the skin or eyes; or pain in the upper stomach area. These may be early symptoms of lactic acidosis or liver problems.

- Serious, even fatal, cases of pancreatitis (inflammation of the pancreas) have been reported with the use of some reverse transcriptase inhibitors, such as Lamivudine. Notify your doctor immediately if you develop symptoms of pancreatitis including nausea, vomiting, diarrhea, abdominal pain, and/or fever.
- Changes in body fat: These changes have happened in patients taking antiretroviral medicines like Lamivudine/ Zidovudine tablets. The changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the 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 at this time.

If you experience any of the following serious side effects, stop taking this combination of Lamivudine and Zidovudine and seek emergency medical attention or notify your doctor immediately:

- an allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives);
- muscle pain or weakness; or
- peripheral neuropathy (nerve damage), which may cause numbness, tingling, or pain.

Other, less serious side effects may be more likely to occur.

- mild nausea, vomiting, diarrhea, or decreased appetite;
- a headache;
- dizziness;
- depression/anxiety
- myalgia
- fever
- insomnia

Side effects other than those listed here may also occur. Talk to your doctor about any side effect that seems unusual or that is especially bothersome.

### **Nevirapine can cause**

- Serious liver damage and skin reactions that can cause death. Any patient can experience such side effects, but some patients are more at risk than others. (See "What is the most important information I should know about Lamivudine/Zidovudine tablets co-packaged with Nevirapine tablets?" at the beginning of this Medication Guide.)
- Other common side effects of Nevirapine include nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain, and myalgia. This list of side effects is not complete. Ask your doctor or pharmacist for more information.
- Changes in body fat have also been seen in some patients taking antiretroviral therapy. The changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the 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 at this time.

### **How do I store these medications?**

Store at room temperature, between 59° to 86°F (15° to 30°C). Throw away medicines that are no longer needed or out-of-date. Keep all medicines out of the reach of children.

### **General information**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use these medications for a condition for which it was not prescribed. Do not give these medications to other people, even if they have the same condition you have. It may harm them.

This Medication Guide summarizes the most important information about Lamivudine/Zidovudine tablets co-packaged with Nevirapine tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about these medications.

### **What are the ingredients in Lamivudine/ Zidovudine tablets co-packaged with Nevirapine tablets?**

**Active ingredients:** Lamivudine, Zidovudine and Nevirapine.

#### **Inactive ingredients:**

**Lamivudine/Zidovudine tablets:** The inactive ingredients in the Lamivudine /Zidovudine tablet includes microcrystalline cellulose, sodium starch glycolate,

povidone, colloidal silicon dioxide, talc, magnesium stearate, colour opadry white(Y-1-7000), purified water and isopropyl alcohol

**Nevirapine Tablets:** The inactive ingredients in the nevirapine tablet include microcrystalline cellulose, lactose, croscarmellose sodium, povidone, colloidal anhydrous silica, purified talc, magnesium stearate and purified water.

**For additional information contact**

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