



National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

**SUMMARY OF PRODUCT CHARACTERISTICS
(SmPC) TEMPLATE**

1. NAME OF THE MEDICINAL PRODUCT

LAMIVUDINE / NEVIRAPINE / ZIDOVUDINE TABLETS 150 mg / 200 mg / 300mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LABEL CLAIM

Each film coated tablet contains:

Lamivudine USP	150 mg
Nevirapine USP	200 mg
Zidovudine USP	300 mg

List of excipients

Lactose monohydrate, Microcrystalline cellulose, Povidone, Colloidal silicon dioxide, Sodium starch glycolate, Magnesium stearate, Film coating: FD&C Blue # 2 Aluminium Lake, hypromellose, Titanium dioxide and triacetin.

3. PHARMACEUTICAL FORM

Immediate release, film coated, tablets (solid oral dosage form)

DESCRIPTION: Blue colored, capsule shaped, biconvex, film coated tablets, debossed with “M” and “104” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC indications

Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, and for children that weigh at least 25 kg.

This fixed combination replaces the three components (lamivudine, nevirapine and zidovudine) used separately in similar dosages. Treatment must be started with lamivudine, zidovudine and nevirapine separately for the first 6-8 weeks until the patient is stable on nevirapine 200 mg twice daily and adequate tolerability to lamivudine, zidovudine and nevirapine has been demonstrated.

4.2 Posology and method of administration

Oral use.

Therapy should be prescribed by a physician experienced in the management of HIV infection.

The recommended dose of Lamivudine / Nevirapine / Zidovudine Tablets in adults and children weighing at least 25 kg is:

- One tablet twice daily.

For situations where discontinuation of therapy with or dose reduction of any of the active substances of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg is necessary, separate preparations of lamivudine, zidovudine and nevirapine are available as tablets/capsules and oral solutions/suspensions.

Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg may be taken with or without food.

Children

Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg is not indicated for children weighing less than 25 kg, since appropriate dose reductions cannot be made.

Elderly

Special care is advised in this age group due to associated changes such as decrease in renal function and alteration of haematological parameters.

Dose adjustment

Renal Impairment

Since different dose adjustments for either compound may be necessary in patients with renal impairment (creatinine clearance ≤ 50 ml/min), it is recommended that separate preparations of lamivudine, zidovudine and nevirapine be administered.

Hepatic impairment

No dose adjustments are necessary for mild to moderate hepatic impairment.

In patients with severe hepatic impairment Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg must not be used, since nevirapine is contraindicated.

Haematological adverse reactions

Since substitution or dose reductions of zidovudine should be considered in patients whose haemoglobin concentrations or neutrophil counts fall to clinically significant levels, it is recommended that separate preparations of lamivudine, nevirapine and (if appropriate) zidovudine be administered.

Discontinuation and reintroduction of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg

Special consideration should be given to the safe discontinuation of therapy with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg. In patients having interrupted treatment with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg for more than two weeks, therapy should be reintroduced with separate formulations of lamivudine, zidovudine and nevirapine with a dose escalation period for nevirapine of 200 mg once daily for 14 days, then a 200 mg twice daily regimen. Only when the patient is stable on this triple combination, therapy with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg may be resumed.

4.3 Contraindications

Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg is contraindicated in patients with

- Hypersensitivity to lamivudine, nevirapine, zidovudine or to any of the excipients contained in the formulation.
- abnormally low neutrophil counts ($< 0.75 \times 10^9/l$).
- abnormally low haemoglobin levels (< 7.5 g/dl or 4.65 mmol/l).
- severe hepatic impairment (Child-Pugh C or ALT or AST values > 5 upper limit of normal [ULN])
- history of severe rash, rash accompanied by constitutional symptoms or liver toxicity due to nevirapine.

Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg must not be used concomitantly with rifampicin or herbal preparations containing St. John's Wort (*Hypericum perforatum*).

4.4 Special warnings and special precautions for use

Dose adjustments

It is recommended that separate preparations of lamivudine, zidovudine and nevirapine be administered when any dosage adjustment is necessary. In these cases the health care provider should refer to the individual prescribing information of these medicinal products.

Opportunistic infections

Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of HIV infection.

Transmission of HIV

Treatment with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg has not been shown to eliminate the risk of transmission of HIV infection by sexual contact or by blood transfer, although the risk may be reduced. Patients should continue to use appropriate precautions to prevent transmission of HIV.

Liver disease

Severe and life-threatening liver toxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. This has mainly occurred during the initial 6 weeks of therapy but may occur up to 18 weeks after start of nevirapine. Nevirapine-associated liver toxicity is a hypersensitivity reaction, thought to be immune mediated, which may or may not be associated with a cutaneous reaction (rash) and/or constitutional symptoms, including fever, arthralgia, myalgia and general malaise. Factors linked to nevirapine-associated liver toxicity are female sex, higher baseline CD4 counts, higher baseline levels of alanine aminotransferase, hepatitis C co-infection and alcohol abuse. Women with CD4 cell counts >250 cells/mm³ had a 12-fold higher risk of symptomatic liver toxicity compared to women with CD4 counts <250 cells/mm³. A 5-fold increased risk was observed in men with CD4 counts > 400 cells/mm³. Unless the benefit outweighs the risk treatment with nevirapine should not be initiated in adult females with CD4 cell counts greater than 250 cells/mm³ or in adult males with CD4 cell counts greater than 400 cells/mm³.

Monitoring of liver transaminases should be performed if the patient experiences signs or symptoms suggestive of liver toxicity (e.g. anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness).

Patients developing signs or symptoms of liver toxicity and/or hypersensitivity should promptly seek medical evaluation. Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg and any other nevirapine-containing products must be permanently discontinued in any patient experiencing severe liver toxicity.

Caution should be exercised when administering Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg to any patient with chronic hepatitis B infection. Specifically, lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication. Discontinuation of lamivudine or virologic failure after development of resistance to lamivudine by HBV may cause hepatic deterioration and a hepatitis flare. If Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg is discontinued in a patient with HBV infection, the patient should be periodically monitored, both clinically and by assessment of liver function tests (ALT and bilirubin levels) and markers of HBV replication, for at least four months, and then as clinically indicated.

Patients with chronic hepatitis B and C that are treated with combination antiretroviral therapy, have an increased risk of severe and potentially fatal hepatic adverse events.

Patients with pre-existing liver dysfunction have an increased frequency of liver function abnormalities during combination ART, and should be monitored according to current standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of therapy should be considered.

Skin reactions

Rash is a common adverse reaction to nevirapine. Cases are usually mild to moderate but severe and life-threatening skin reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred. These have mainly been reported during the initial 6 weeks of therapy, but may occur up to 18 weeks after start of nevirapine. Patients should be warned to report symptoms of a hypersensitivity reaction immediately (e.g. fever, rash, arthralgias or myalgias). Nevirapine must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by systemic symptoms.

Neither prednisone nor antihistamines decrease the incidence of nevirapine-associated rash. Factors linked to nevirapine-associated rash are higher baseline CD4 count, higher baseline HIV RNA level, female sex, higher age and higher nevirapine concentration. Furthermore, failure to follow the initial dosing of 200 mg nevirapine daily during the lead-in period and a long delay between the initial symptoms and medical consultation are risk factors for developing serious cutaneous reactions. Patients with a rash should be assessed for liver toxicity, and nevirapine must be permanently discontinued if the liver transaminases are elevated. Nevirapine must not be restarted following severe skin reactions.

Discontinuation and reintroduction of nevirapine-containing preparations, such as Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg

Because nevirapine is an inducer of drug-metabolizing hepatic enzymes, administration of full therapeutic doses of nevirapine without a two-week, low-dose escalation phase may result in excess plasma drug levels and potentially increase the risk for toxicity. Therefore, in a patient who has interrupted treatment with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg for more than two weeks and is to be restarted later, therapy should be reintroduced with separate formulations of lamivudine, zidovudine and nevirapine with a dose escalation period of 200 mg nevirapine once daily for 14 days, then a 200 mg twice-daily regimen. Only when the patient is stable on this triple combination, therapy with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg may be resumed. Due to the long half life of nevirapine, discontinuation of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg without immediate institution of another effective antiretroviral therapy, will lead to a period of *de facto* nevirapine monotherapy. Since nevirapine has a low barrier of resistance, this may lead to high-level nevirapine resistance. There is no validated strategy for handling this risk. However, covering the slow nevirapine elimination after discontinuation with 2-4 weeks of boosted PI monotherapy, in case a new antiretroviral regimen is not immediately instituted, has been suggested.

Haematological adverse reactions

Anaemia, neutropenia and leucopenia have been reported in patients receiving zidovudine-containing preparations, especially in patients with advanced HIV disease (poor bone marrow reserve) or low serum vitamin B12 levels, and usually after at least 4-6 weeks of therapy.

Therefore, it is recommended to monitor haematological parameters in patients receiving Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg, e.g. as follows:

- In advanced HIV disease: at least every two weeks during the first three months of zidovudine therapy, and monthly thereafter.
- In early (non-symptomatic) HIV disease, at a frequency depending on the overall condition of the patient: e.g. every one to three months.

Since substitution, dose reduction or interruption of zidovudine therapy may be necessary in patients whose haemoglobin concentrations or neutrophil counts fall to clinically significant levels, separate preparations of lamivudine, nevirapine and (if appropriate) zidovudine should be administered (refer to the Summary of Product Characteristics of zidovudine-only containing products).

Lactic acidosis

Lactic acidosis is a rare but severe, potentially life-threatening complication associated with NRTI use. It may occur after a few to several months of treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity. Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs, including zidovudine/lamivudine. Lactic acid levels > 10 mmol/l usually are a medical emergency.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative

infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia and neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether these neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These considerations, however, do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. A higher risk of lipodystrophy has been associated e.g. with older age of the patient, longer duration of ART and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered.

Immune Reactivation Syndrome

In HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, *Pneumocystis pneumonia*) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary.

Osteonecrosis

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination ART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Pancreatitis

Treatment with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur. Patients with a high risk of pancreatitis or those receiving also other products known to be associated with pancreatitis should be closely followed for symptoms of this condition.

4.5 Interaction with other medicinal products and other forms of interaction

As Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg contains lamivudine, zidovudine and nevirapine, any interactions that have been identified with these agents individually may occur with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg. Whereas lamivudine is almost completely eliminated unchanged via the kidneys, zidovudine and nevirapine undergo hepatic metabolism. Zidovudine is eliminated after biotransformation to an inactive glucuronidated metabolite; nevirapine is extensively biotransformed by hepatic cytochrome P4503A4 (CYP4503A) and CYP2B6 isoenzymes prior to excretion.

Lamivudine and zidovudine do not inhibit the cytochrome P450 isoform CYP3A.

Nevirapine is an inducer of the hepatic cytochrome P450 enzymes with maximal induction occurring within 2-4 weeks after initiating full dose therapy. Thus, principally interactions with all medicinal products metabolized by this pathway or inducing/inhibiting these isoenzymes may occur. Caution is warranted, when administering these agents concomitantly with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg especially when they have a small therapeutic margin.

The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised.

Concomitant treatment with therapeutic doses of dapsone (which may cause haemolytic anaemia) or of potentially nephrotoxic or myelosuppressive agents (e.g. systemic pentamidine, pyrimethamine, cotrimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine. If concomitant therapy with any of these drugs is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dose of the concomitantly administered drug should be reduced. If modification of the zidovudine dosage is necessary, separate preparations of lamivudine, zidovudine and nevirapine should be administered.

Clinical data do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole, aerosolized pentamidine, pyrimethamine, dapsone and aciclovir at the doses used in prophylaxis of opportunistic infections.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg
INFECTION		
<i>Antiretrovirals</i>		
<i>Nucleoside analogues</i>		
Didanosine / Nevirapine / Lamivudine / Zidovudine Tenofovir / Nevirapine / Lamivudine / Zidovudine Abacavir / Nevirapine / Lamivudine / Zidovudine	No interaction	
Emtricitabine / Lamivudine		Because of overlapping resistance and lack of additive antiretroviral effects, Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg should not be co-administered with emtricitabine.
Stavudine/ Zidovudine		Due to no additive effect <i>in vivo</i> , and antagonism <i>in vitro</i> , stavudine should not be co-administered with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg.
<i>Non-nucleoside analogues</i>		

Efavirenz/Nevirapine		Concomitant use is not recommended for additive toxicity and no benefit in terms of efficacy.
Protease inhibitors		
Fosamprenavir (1400 mg b.i.d) / Nevirapine	Amprenavir AUC _{ss} ↓ 37% C _{min} ↓ 39% (historical controls)	Unboosted fosamprenavir and Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg should not be co-administered.
Fosamprenavir/rtv (700 / 100 mg b.i.d) / Nevirapine / Zidovudine / Lamivudine	Amprenavir AUC _{ss} ↓ 11% C _{min} ↓ 19% (historical controls)	No dose adjustment is recommended, when Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg is co-administered with fosamprenavir/rtv.
Saquinavir (HGC) / rtv / Nevirapine	No data available	
Indinavir (800 mg q8h) / Nevirapine	Indinavir: AUC ↓ mean 31%, C _{min} ↓ mean 44% Nevirapine: ↔	Concomitant treatment of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg with unboosted indinavir is not recommended. Concomitant treatment with ritonavir-boosted indinavir is recommended only if therapeutic drug monitoring (TDM) is available.
Ritonavir (rtv, 600 mg bid) / Nevirapine / Zidovudine / Lamivudine	No interaction	
Nelfinavir (750 mg tid) / Nevirapine	Nelfinavir: (+ active metabolite): AUC ↓ mean 20%, C _{min} ↓ mean 35%	A dose increase of nelfinavir may be mandated. Concomitant treatment recommended only if TDM is available.
Lopinavir/rtv (400/100 mg capsules bid) / Nevirapine	Lopinavir: AUC ↓ mean 27%, C _{min} ↓ mean 44% No data available for lopinavir/rtv tablets	The dose of lopinavir/rtv should be increased to 533/133 mg (4 capsules bid with food), when co-administered with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg. A dose increase of lopinavir/rtv may be

		mandated. Concomitant treatment of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg with lopinavir/rtv tablets is recommended only if TDM is available.
Atazanavir/rtv (300 / 100 mg) / Nevirapine	Atazanavir : AUC ↓ mean 40% C _{min} ↓ 78%	Concomitant use of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg and atazanavir/rtv is not recommended.
Tipranavir/rtv (various doses) / Nevirapine	Nevirapine: AUC ↓ 0-25%	Concomitant use of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg and tipranavir/rtv not recommended due to possibly additive hepatotoxicity.
Darunavir/rtv (300 - 400 / 100 mg b.i.d) / Nevirapine / Zidovudine / Lamivudine	No significant interaction	
Ribavirin/ Zidovudine		Due to additive/synergistic bone marrow toxicity, zidovudine should be replaced by an alternative agent in patients treated with ribavirin. Therefore, Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg should not be used in this situation.
Antifungals		
Ketoconazole (400 mg q.d. steady state) / Nevirapine	Ketoconazole: AUC ↓ mean 72%, C _{max} ↓ mean 44% Nevirapine: AUC ↑ 15-28%	Concomitant use of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg and ketoconazole is not recommended. Similar decreases of itraconazole concentrations are possible.

<p>Fluconazole / Nevirapine</p> <p style="text-align: center;">/ Zidovudine</p>	<p>Fluconazole pk ↔ Nevirapine: AUC ↑ ≈ 100% Zidovudine: AUC ↑ 74%</p>	<p>When Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg is given concurrently with fluconazole, patients should be monitored closely for signs of toxicity of nevirapine and zidovudine.</p>
Antibacterials/Antituberculotics		
<p>Clarithromycin / Nevirapine</p> <p style="text-align: center;">/ Zidovudine</p>	<p>Clarithromycin: AUC ↓ mean 31% C_{min} ↓ mean 56% 14-OH Clarithromycin (active metabolite): AUC ↑ mean 42% C_{max} ↑ mean 47% Nevirapine: AUC ↑ mean 26% C_{min} ↑ mean 28% C_{max} ↑ mean 24%</p>	<p>The clinical significance of the pharmacokinetic interaction is unknown. On co-administration of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg, no dose adjustment is recommended. However, if possible, consider using azithromycin instead of clarithromycin.</p> <p>Clarithromycin tablets reduce the absorption of zidovudine. The clinical relevance is unclear. However, this effect can be avoided by separating the administration of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg and clarithromycin by at least two hours.</p>
<p>Rifampicin (Rifampicin at steady state) / Nevirapine</p> <p style="text-align: center;">/ Zidovudine</p>	<p>Rifampicin: pk ↔ Nevirapine: AUC ↓ mean 58% C_{min} ↓ mean 68% C_{max} ↓ mean 50%</p> <p>Zidovudine: AUC ↓, mean 47%</p>	<p>Since neither appropriate doses of nevirapine, when given concomitantly with rifampicin, nor the safety of this combination have been established, concomitant use of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg and rifampicin is not recommended.</p>
<p>Rifabutin / Nevirapine (both at steady state)</p>	<p>Rifabutin: AUC ↑ mean 17% C_{max} ↑ mean 28% 25-O-desacetyl-rifabutin (active metabolite): AUC ↑ mean 24% C_{max} ↑ mean 29% Nevirapine: pk ↔</p>	<p>Due to high intersubject variability large increases in rifabutin exposure with the risk of higher rifabutin toxicity may occur in some patients. Caution should be used in concomitant administration of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg /</p>

		200 mg / 300 mg and rifabutin.
Trimethoprim/Sulfamethoxazole / Lamivudine	Lamivudine AUC ↑ 40%	No dosage adjustment is necessary, unless the patient has renal impairment.
Antimalarials		
Chloroquine / Nevirapine Mefloquine / Nevirapine Proguanil / Nevirapine Sulfadoxine / Nevirapine Pyrimethamine / Nevirapine	No formal interaction studies available	Drug interactions and safety in co-administration with nevirapine have not been systematically evaluated. On a theoretical basis, clinically significant drug interactions with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg are unlikely.
Amodiaquine / Artesunate 600/250 mg q.d.) / Nevirapine	No formal interaction study available	Co-treatment should be done with caution.
Artemisinin and its derivatives / Nevirapine	No formal interaction study available	Artemisinin and its derivatives are transformed into active metabolites by CYP3A. Exposure may be decreased by nevirapine. Empirical data are lacking and possible clinical consequences are unknown.
Atovaquone / Nevirapine / Zidovudine	No formal interaction studies available Zidovudine AUC ↑ 30-35%	Drug interactions and safety in co-administration with nevirapine has not been systematically evaluated; on a theoretical basis, clinically significant drug interactions with nevirapine are unlikely. No dose adjustment is necessary, when Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg is used concomitantly with atovaquone.
Quinine / Nevirapine	No formal interaction study available	Quinine is extensively metabolised by CYP3A. Co-administration with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg may decrease quinine exposure, and reduce antimalarial effect.
Lumefantrine / Nevirapine Halofantrine / Nevirapine	No formal interaction study available	These agents are metabolised by CYP3A. Hence, co-treatment with nevirapine may decrease exposure. Co-treatment of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300

		mg with these agents is not recommended.
Anticonvulsants		
Phenytoin / Nevirapine / Zidovudine	No formal interaction study available Case reports have described increases as well as decreases of phenytoin plasma levels in co-treatment with Zidovudine	Phenytoin and nevirapine clearances are likely to be increased. Co-administration with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg should be avoided unless plasma concentrations of phenytoin and nevirapine can be monitored.
Valproic acid / Nevirapine Valproic acid (250 - 500 t.i.d) / Zidovudine	No formal interaction study available Zidovudine: AUC ↑ 80%	If co-administered with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg, plasma concentrations of valproic acid should be monitored and patients should be controlled for haematological toxicity.
CONTRACEPTION		
Hormonal contraceptives		
Ethinylestradiol / Norethindrone (EE 00.35 mg / NET 1.0 mg, single dose) / Nevirapine (at steady state)	EE: AUC ↓ mean 20% NET: AUC ↓ mean 19% C _{max} : ↓ mean 16%	Appropriate doses for hormonal contraceptives (except for DMPA as detailed below) in combination with nevirapine with respect to efficacy and safety have not been established. Concomitant use of hormonal contraceptives other than DMPA with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg is not recommended.

DMPA / Nevirapine (at steady state)	DMPA: Pk ↔ Nevirapine: AUC ↑ 20%	No dose adjustment of nevirapine required. Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg can be used concomitantly with DMPA.
OTHERS		
Methadone / Nevirapine / Zidovudine	Methadone: AUC ↓ mean 65% C _{max} ↓ mean 50% Zidovudine: AUC ↑ 29-43%	Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of narcotic withdrawal symptoms and methadone dose should be adjusted accordingly. No dose alteration of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg is necessary when used concomitantly with methadone.
Warfarin/Nevirapine	Complex interaction with potential for both, increases and more likely decreases in coagulation time.	Close monitoring of coagulation is warranted, since the net effect of the interaction may change during the first weeks of co-administration or upon discontinuation of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg.
St. John's Wort (<i>Hypericum perforatum</i>) / Nevirapine	No formal interaction study available	Since co-administration of St John's Wort and nevirapine is expected to significantly lower nevirapine exposure, co-administration of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg and St John's Wort is contraindicated.
Probenecid/ Zidovudine	Zidovudine: AUC ↑ 100-200%	Co-administration should be avoided.

4.6 Pregnancy and lactation

Pregnancy: No increased risk of birth defects has been reported for lamivudine, zidovudine or nevirapine. However, risks to the fetus cannot be ruled out.

Nursing Mothers: Lamivudine, zidovudine and nevirapine are excreted into the breast milk of lactating mothers. Recent data indicate that breastfeeding may not have to be discouraged when certain conditions are fulfilled, e.g. when mother and/or child receive effective antiretroviral therapy. The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted before advising patients on this matter.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

As Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg contains lamivudine, zidovudine and nevirapine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of additional toxicity due to the concurrent administration of the three agents.

The most frequently reported adverse reactions are rash, headache, nausea, diarrhoea, abdominal pain and myalgia. The most common serious adverse reactions include anaemia (which may require transfusions), neutropenia, leucopenia, hypersensitivity reactions, and hepatic toxicity.

Adverse events considered to be at least possibly related to treatment with zidovudine, lamivudine and nevirapine, are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$) or very rare ($\leq 1/10,000$).

In addition, adverse events identified during post-approval use of lamivudine, zidovudine, lamivudine/zidovudine as a fixed-dose combination and/or nevirapine are listed. Since they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made (frequency category: 'not known'). These events have been included for the potential causal connection to lamivudine and/or zidovudine and/or nevirapine, taking also into account their seriousness and the number of reports.

Blood and lymphatic systems disorders

Common: Anaemia, neutropenia, leucopenia

Uncommon: Thrombocytopenia, pancytopenia

Rare: Pure red cell aplasia

Very rare: Aplastic anaemia.

Metabolic and nutrition disorders

Rare: Lactic acidosis

Unknown: Changes in distribution of body fat, hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, hyperlactataemia.

Psychiatric disorders

Rare: Anxiety, depression.

Nervous system disorders

Very common: Headache

Common: Dizziness, insomnia

Rare: Paraesthesia, somnolence, loss of mental acuity, convulsions.

Cardiac disorders

Rare: Cardiomyopathy.

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea

Rare: Cough.

Gastrointestinal disorders

Very common: Nausea

Common: Vomiting, abdominal pain and diarrhoea

Uncommon: Flatulence

Rare: Pancreatitis, oral mucosa pigmentation, taste perversion, dyspepsia.

Hepatobiliary disorders

Common: Hepatitis, elevated liver enzymes, alkaline phosphatase and bilirubin

Uncommon: Jaundice

Rare: Liver failure/fulminant hepatitis, severe hepatomegaly with steatosis.

Skin and subcutaneous tissue disorders

Common: Rash (also severe), hair loss

Uncommon: Stevens-Johnson syndrome, urticaria, pruritus

Rare: Toxic epidermal necrolysis, angio-oedema, nail and skin pigmentation, sweating.

Musculoskeletal and connective tissue disorders

Common: Myalgia

Uncommon: Myopathy, osteonecrosis

Rare: Arthralgia.

Renal and urinary disorders

Rare: Urinary frequency.

Reproductive system and breast disorders

Rare: Gynaecomastia.

General disorders and administration site disorders:

Common: Allergic reactions, malaise, fatigue

Uncommon: Asthenia, fever, generalized pain

Rare: Hypersensitivity syndrome, anaphylaxis, chest pain, influenza-like syndrome, chills

Unknown: Immune reconstitution syndrome.

4.9 Overdose

There is limited experience of overdosage with lamivudine/zidovudine. No specific signs and symptoms have been identified following acute overdose with zidovudine or lamivudine apart from those listed as undesirable effects.

Cases of nevirapine overdose at doses ranging from 800 to 6000 mg per day for up to 15 days have been reported. Patients have experienced oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases and weight loss.

No fatalities occurred and the patients recovered. There is no known antidote for any of the three agents. If overdose occurs, patients should be monitored for toxicity and standard supportive treatment applied as necessary. Since elimination of lamivudine and the glucuronide metabolite of zidovudine are enhanced by haemodialysis, continuous haemodialysis could be used in the treatment of overdosage (although this has not been studied).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations.

ATC Code: J05AR05

Mechanism of action

Lamivudine and zidovudine are nucleoside analogues that have activity against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both agents are metabolised intracellularly to their active moieties, lamivudine 5'-triphosphate (TP) and zidovudine 5'-TP respectively. Their main modes of action are as chain terminators of viral reverse transcription.

Lamivudine-TP and zidovudine-TP have selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

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

Clinical efficacy

In clinical trials, combination therapy with lamivudine, zidovudine and nevirapine has been shown to reduce HIV-1 viral load and increase CD4 cell count. Clinical end-point data indicate that lamivudine and zidovudine in combination with nevirapine result in a significant reduction in the risk of disease progression and mortality. In two different randomized trials of zidovudine and lamivudine in combination with nevirapine in ART-naïve patients, 65% and 73% of subjects achieved plasma HIV RNA < 20 copies/ml and < 50 copies/ml, respectively after 1 year by intention to treat analysis.

The combination of lamivudine, zidovudine and nevirapine has not been specifically investigated in HIV patients co-infected with HBV.

Drug resistance

In the great majority of cases when combination antiretroviral therapy comprising zidovudine and lamivudine fails virologically, the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility). Virus with M184V replicates less well than does wild type virus. *In vitro* data tend to suggest that the continuation of lamivudine in anti-retroviral regimens despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered when the activity of the best available NRTI backbone is significantly compromised.

On virological failure, resistance to zidovudine is developed along two separate, though not mutually exclusive, pathways. The first of these include M41L, L210W and T215F/Y. The second includes D67N, K70R and K219E/Q. Collectively, these mutations are termed "thymidine analog mutations" (TAM). In viruses with M184V, two to three TAMs are generally required for phenotypically detectable and clinically significant zidovudine resistance. M41L, L210W, and T215Y have a greater effect on zidovudine susceptibility and cross-resistance to other NRTIs than the other TAMs. Other important mutations selected for by zidovudine include T69 insertion mutations and the Q151M complex, where this mutation appears in combination with mutations at positions 75, 77, and 116. Both of these patterns confer high-level resistance to zidovudine and all other presently available NRTIs.

The likelihood of a gradual accumulation of mutations conferring resistance to the entire class of NRTI, upon virological failure with combination therapy including zidovudine and lamivudine, underscores the importance of early detection of virological failure. Delayed detection of virological failure may severely limit the options for next-line therapy.

The most common resistance mutations selected for by nevirapine are Y181C, K103N and G190A. All of these mutations cause high-level resistance to nevirapine. The vast majority of patients failing nevirapine-containing antiretroviral therapy will have developed one or more mutations conferring high-grade resistance to nevirapine, as well as cross-resistance to efavirenz and delavirdine. Conversely, patients failing therapy including efavirenz or delavirdine will usually have a virus cross-resistant to nevirapine. If failing therapy is continued, further resistance mutations will accumulate. High-level resistance to nevirapine is selected for by a single dose in monotherapy, as has been demonstrated by the high prevalence of resistance mutations following nevirapine use for prevention of mother to child transmission. Due to the long half-life of nevirapine, a period of functional monotherapy with nevirapine may follow upon discontinuation of effective nevirapine-containing antiretroviral therapy. This may cause significant nevirapine resistance, and compromise the efficacy of future nevirapine, efavirenz or delavirdine therapy.

5.2 Pharmacokinetic properties

Absorption

Lamivudine, zidovudine and nevirapine are well absorbed from the gastrointestinal tract. The bioavailability of oral lamivudine in adults is normally between 80 – 85%, for zidovudine 60 – 70% and for nevirapine > 90%.

After single dose administration of Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg in healthy volunteers, the following pharmacokinetic values were obtained:

Pk parameter	Lamivudine [arithm. Mean]	Zidovudine [arithm. Mean]	Nevirapine [arithm. Mean]
AUC _{0-t}	101.49% – 113.82%	91.90% - 105.10%	97.98% - 101.32%
C _{max}	101.70% – 119.04%	81.54% - 120.55%	93.36% - 100.00%
AUC _{0-∞}	101.45% – 113.39%	92.02% - 104.83%	-

*AUC₀₋₇₂ (µg.h/ml) value for nevirapine has been reported.

The extent of lamivudine and zidovudine exposure (AUC_T) and estimates of half-life following administration of a respective fixed combination product (Combivir, GSK) with food were similar when compared to fasting subjects, although the rates of absorption (C_{max}, t_{max}) were slowed. The absorption of nevirapine is not affected by food. Based on these data this product may be administered with or without food.

Distribution

Intravenous studies showed that the mean apparent volume of distribution is 1.3 l/kg for lamivudine, 1.6 l/kg for zidovudine, and 1.2 l/kg for nevirapine.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 36% serum albumin *in vitro*).

The plasma protein binding of zidovudine is 34% to 38%, and is 60% for nevirapine.

Drug interactions involving binding site displacement are not anticipated with this product.

Metabolism

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominantly cleared unchanged by renal excretion. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5 - 10%) and low plasma protein binding.

The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50 – 80% of the administered dose eliminated by renal excretion. 3'-amino-3'-deoxythymidine has been identified as a metabolite of zidovudine following intravenous dosing.

Nevirapine is extensively biotransformed primarily via the cytochrome P450 isozyme CYP3A and CYP2B6. Hydroxylation and glucuronide conjugation are the major routes of metabolism with > 80% of the administered dose being excreted as metabolites in the urine. Nevirapine is an inducer of hepatic P450 enzymes, also leading to autoinduction with increased nevirapine clearance and decreased plasma half-life after two to four weeks of dosing.

Elimination

The observed lamivudine half-life of elimination is 5 to 7 hours. The half-life of intracellular lamivudine triphosphate has been estimated to approximately 22 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%), including tubular secretion through the organic cationic transport system. Studies in patients with renal impairment show that lamivudine elimination is affected by renal dysfunction.

In studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6 l/h/kg. The half-life of intracellular zidovudine triphosphate has been estimated to around 7 hours. Renal clearance of zidovudine is estimated to be 0.34 l/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

The mean terminal plasma half-life of nevirapine is 45 hours after single dose and approximately 25-30 hours following multiple doses (200-400 mg). A large fraction of nevirapine is renally eliminated as conjugates with less than 5% being excreted unchanged through the kidneys and about 10% via faeces.

Special populations

Paediatrics: In general, lamivudine pharmacokinetics in paediatric patients are similar to those in adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age.

The data available on the pharmacokinetics in neonates and young infants indicate that glucuronidation of zidovudine is reduced with a consequent increase in bioavailability, reduction in clearance and longer half-life in infants less than 14 days old but thereafter the pharmacokinetics appear similar to those reported in adults.

Pregnancy: The pharmacokinetics of lamivudine and zidovudine were similar to that of non-pregnant women. Nevirapine clearance has been shown to be increased in pregnant women resulting in lower AUC and C_{max} levels as compared to non-pregnant women. The clinical relevance of this finding is currently unknown.

5.3 Preclinical safety data

Lamivudine/Zidovudine

Neither lamivudine nor zidovudine is mutagenic in bacterial tests, but like many nucleoside analogues they show activity in *in vitro* mammalian tests such as the mouse lymphoma assay. Lamivudine has not shown any genotoxic activity in *in vivo* studies at doses that gave plasma concentrations up to 40 - 50 times higher than clinical plasma levels. Zidovudine showed clastogenic effects in an oral repeated dose micronucleus test in mice.

A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at exposures equivalent to those seen in humans. That study demonstrated that fetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

The carcinogenic potential of a combination of lamivudine and zidovudine has not been tested.

In oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential. In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. A subsequent intravaginal carcinogenicity study confirmed the hypothesis that the vaginal tumours were the result of long-term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine. There were no other zidovudine-related tumours observed in either sex of either species.

In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study zidovudine was administered at maximum tolerated doses to pregnant mice from day 12 to 18 of gestation. One year post-natally, there was an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight).

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months, with exposure beginning prenatally on gestation day 10. Treatment related findings were limited to late

occurring vaginal epithelial tumours, which were seen with a similar incidence and time of onset as in the standard oral carcinogenicity study. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.

In reproductive toxicity studies lamivudine has demonstrated evidence of causing an increase in early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in man, but not in the rat even at very high systemic exposure. Zidovudine had a similar effect in both species, but only at very high systemic exposures. Lamivudine was not teratogenic in animal studies. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations, but no evidence of foetal abnormalities was observed at lower doses.

Nevirapine

Preclinical data revealed no special hazard for humans other than those observed in clinical studies based on conventional studies of safety, pharmacology, repeated dose toxicity, and genotoxicity. In reproductive toxicology studies, evidence of impaired fertility was seen in rats. In carcinogenicity studies, nevirapine induced hepatic tumours in rats and mice. In rats these findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action. The mechanism of tumours in mice is not yet clarified and therefore their relevance in humans remains to be determined.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Microcrystalline cellulose, Povidone, Colloidal silicon dioxide, Sodium starch glycolate, Magnesium stearate, Film coating: FD&C Blue # 2 Aluminium Lake, hypromellose, Titanium dioxide and triacetin

6.3 Shelf life

60 Months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package. Protect from light.

6.5 Nature and contents of container

Pack:

HDPE bottle of 60's

Reference list:

This text is primarily based on the European SPCs for Combivir and Viramune, available at:

<http://www.emea.europa.eu/humandocs/PDFs/EPAR/combivir/H-190-PI-en.pdf> ,

<http://www.emea.europa.eu/humandocs/PDFs/EPAR/viramune/H-183-PI-en.pdf>

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Section 4.8

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7. APPLICANT/MANUFACTURER

Marketing Authorization Holder

HEALTHLINE LIMITED

Manufactured by

Manufactured at
Mylan Laboratories Limited
Plot No H-12 & H-13, MIDC, WALUJ,

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Maharashtra, INDIA.