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

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: FDC Blue # 2 Aluminium Lake, Hypromellose, Titanium dioxide and Talcum.

CLINICAL PARTICULARS

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 tablet, first one-component lamivudine, nevirapine and zidovudine is recommended in similar dosages. Treatment must be started with lamivudine, zidovudine and nevirapine especially for the first 2-4 weeks until the patient is stable on nevirapine (200 mg twice daily) and single dose lamivudine. In lamivudine, zidovudine and nevirapine has been demonstrated.

Posology and method of administration
Dosage
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 adultsno intermediate dose titration 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/syrups.
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 recommended in children weighing less than 25 kg, since appropriate dose reductions cannot be made.
Adults
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 renal dose adjustments for either component 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 who may be infected with hepatitis B virus. 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 patients analgesic tolerance to the combination therapy with Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg may be resumed.

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.
- severe hepatic impairment (Child-Pugh Score ≥ 10).
- severe renal impairment (CrCl < 30 ml/min).
- severe haematological disorders (e.g. anaemia (Hb < 7.5 g/dl), neutropenia (ANC < 0.75 x 10⁹/l) and thrombocytopenia (platelet count < 50 x 10⁹/l).
- severe hepatic impairment (Child-Pugh Score ≥ 10) or AST or ALT values > 5 upper limit of normal (ULN).
- History of severe rash, rash accompanied by vesicle/bleed symptoms or if rash recurs on re-challenge.

Lamivudine / Nevirapine / Zidovudine Tablets 150 mg / 200 mg / 300 mg must not be used concomitantly with stavudine or tenofovir disoproxil fumarate (e.g. Adefovir dipivoxil) (Hepatitis B infection).

Special warnings and special precautions for use
Dose adjustment
It is recommended that separate preparations of lamivudine, zidovudine and nevirapine be administered when any dosage adjustment is necessary. In these cases the user 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 AIDS-related illnesses.
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 to 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 hepatic hepatitis, has occurred in patients treated with nevirapine. There has also been a report concerning the death 4 weeks of therapy that may occur in the 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 accompanied with a cutaneous reaction (rash) and/or constitutional symptoms, including fever, arthralgia, malaise and general malaise. Hepatic lesions to nevirapine-associated liver toxicity are limited, very focal and with no zone of necrosis. Severe liver toxicity, including fatal hepatic hepatitis, has occurred in women with CD4 counts >250 cells/mm³ and a Child-Pugh score of appropriately liver toxicity occurred in women with CD4 counts >250 cells/mm³, a 5-fold increased risk was observed in men with CD4 counts > 400 cells/mm³. Using the lowest nevirapine the risk treatment with nevirapine in women 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 transaminase should be performed if the patient experiences signs or symptoms suggestive of liver toxicity (e.g., anorexia, nausea, jaundice, malaise, pruritus, hepatomegaly, tenderness, fever).
Patients developing signs or symptoms of liver toxicity and/or hypersensitivity should promptly seek medical attention and should be evaluated for liver function and for signs of hypersensitivity. Nevirapine should not be prescribed to patients who have experienced nevirapine-associated hepatotoxicity.
Caution should be exercised when administering Lamivudine/Nevirapine/Zidovudine Tablets 150 mg/200 mg/300 mg to any patient with chronic hepatitis B infection. Special care for Lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication. Discontinuation of lamivudine or nevirapine taken after development of resistance to lamivudine by HBV may result in hepatitis exacerbation and nevirapine (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 laboratory examinations, for at least several months. Hepatitis (A) and (B)-induced liver exacerbation in AIDS exacerbation, 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 ARV, 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 mostly been reported during the initial 6 weeks of therapy, but may occur up to 18 weeks after start of nevirapine. Rash associated with blisters, fever, or involvement of any mucosal membrane should be treated as a severe rash or reaction. Nevirapine must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by systemic symptoms.
Neither prednisone nor corticosteroids 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, risk to follow the initial dosing of 200 mg nevirapine daily during the lead-in period and 2 weeks after the beginning of the initial symptoms and increased concentration are risk factors for developing serious cutaneous reactions.
Patients who experience rash must be assessed for liver toxicity, and nevirapine must be permanently discontinued if the patient experiences rash with liver toxicity.
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 lead-in period of 200 mg daily for 14 days is associated with a greater incidence of rash and may 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 reintroduced, therapy should be administered with separate formulations of lamivudine, zidovudine and nevirapine with a dose escalation period of nevirapine of 200 mg once daily for 14 days, then a 200 mg twice daily regimen. Only when the patients analgesic tolerance to the 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