**Attachment 1: Draft WHO Model Formulary (2007) entry for Zidovudine plus Lamivudine plus Nevirapine.**

Source: http://mednet3.who.int/EMLib/modelFormulary/modelFormulary.asp

The following is also based on Product Information for Douvir-N (a fixed combination dose of zidovudine, lamivudine and nevirapine). (http://www.inhousepharmacy.com/hiv/duovir-n.html).

**Name:**

Zidovudine (Azidothymidine, AZT, ZDV)
PLUS
Lamivudine
PLUS
Nevirapine.

**Composition:**

Each film-coated tablet contains:
Lamivudine ..... 150 mg
Zidovudine USP ..... 300 mg
Nevirapine ..... 200 mg
Colour: Titanium Dioxide

**Use:**

**Zidovudine plus lamivudine plus nevirapine:**
The fixed combination is indicated for the treatment of HIV infection, once patients have been stabilized on the maintenance regimen of nevirapine 200 mg bd, and have demonstrated adequate tolerability to nevirapine.

Both zidovudine and lamivudine belong to the nucleoside analogue class of antiretroviral drugs. Both drugs act by terminating the growth of the DNA chain and inhibiting the reverse transcriptase enzyme of HIV. Nevirapine is a non-nucleoside reverse transcriptase inhibitor. It acts by directly inhibiting reverse transcriptase.

**Dose:**

**Zidovudine plus lamivudine plus nevirapine:**
*Adults:* 1 tablet twice daily. The fixed combination should not be administered to patients who have just initiated therapy with nevirapine. This is because an initial lead-in dosing of 200 mg nevirapine once daily for 2 weeks is recommended. Following this lead-in dose, a dose escalation (maintenance dose) to 200 mg nevirapine bd may be carried out in the absence of any hypersensitivity reactions (e.g. rash, liver function test abnormalities; see Warnings and Precautions).

**Contraindications:**

**Zidovudine plus lamivudine plus nevirapine:**
The fixed combination is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the formulation. The fixed dose combination is also contraindicated for patients who are just initiating therapy with nevirapine. These patients require a lead-in dose of nevirapine 200 mg o.d., whereas this formulation contains the maintenance dose of nevirapine 200 mg b.d. (see Uses).

**Nevirapine:**
Severe hepatic impairment; post-exposure prophylaxis.

**Precautions:**

**Zidovudine plus lamivudine plus nevirapine:**

*Lactic acidosis/severe hepatomegaly with steatosis*
Lactic acidosis/severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including stavudine and lamivudine. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering zidovudine and lamivudine to any patient, and particularly to those with known risk factors for liver disease. Cases have also been reported in patients with no known risk factors. Treatment should be discontinued in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis), even in the absence of marked amino-transferase elevations.

*Bone marrow suppression*
The fixed combination should be used in caution in patients who have bone marrow compromise evidenced by granulocyte count < 1000 cells/mm3 or hemoglobin < 9.5 g/dl.

*Myopathy*
Myopathy and myositis, with pathological changes similar to that produced by HIV disease, have been associated with prolonged use of zidovudine.

*Patients with HIV and hepatitis B virus coinfection*
In clinical trials, some patients with HIV infection who have chronic liver disease due to hepatitis B virus infection experienced clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine. Consequences may be more severe in patients with decompensated liver disease.

*Hypersensitivity 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 (including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise and/or significant hepatic abnormalities must discontinue nevirapine as soon as possible. Nevirapine therapy must be initiated with a 14-day lead - in period of 200 mg/day (4 mg/kg/day in paediatric patients), which has been shown to reduce the frequency of rash. If rash is observed during this lead-in period, dose escalation and administration of the fixed dose should not occur until the rash has resolved (See Dosage and Administration).
Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis (transaminase elevations, with or without hyperbilirubinemia, prolonged partial thromboplastin time, or eosinophilia), has occurred in patients treated with nevirapine. Some of these cases began in the first few weeks of therapy, and some were accompanied by rash. Nevirapine administration should be interrupted in patients experiencing moderate or severe ALT or AST abnormalities until these return to baseline values. Nevirapine should be permanently discontinued if liver function abnormalities recur upon readministration. Monitoring of ALT and AST is strongly recommended, especially during the first six months of nevirapine treatment (See Side Effects and Dosage).

**Adverse effects:**

**Lamivudine*:***
Pancreatitis has been reported with the use of lamivudine.
Lactic acidosis and hepatic steatosis, hepatitis and liver failure have been reported with the use of antiretroviral nucleoside analogs, alone or in combination. Other side effects associated with the use of lamivudine are diarrhea, malaise and fatigue, headache, nausea and vomiting, abdominal pain and discomfort, peripheral neuropathy, arthralgias, myalgias, skin rash, pruritus, transient neutropenia and thrombocytopenia and rarely, pancreatitis. Transiently elevated levels of hepatic enzymes and bilirubin (> 5 times the normal level) have also been observed occasionally during treatment with the drug. Resolution of transient neutropenia and raised hepatic and bilirubin levels occurred without dosage modification or discontinuation of therapy.

**Zidovudine*;***
The anaemia reported in patients with advanced HIV disease receiving zidovudine appears to be the result of impaired erythrocyte maturation. Thrombocytopenia has also been reported in patients with advanced disease. Mild drug-associated elevations in total bilirubin levels have been reported as an uncommon occurrence in patients treated for asymptomatic HIV infection.
Clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with 1,500 mg/day of zidovudine were: fever, headache, nausea, vomiting, anorexia, myalgia, insomnia, dizziness, paraesthesias, dyspnoea and rash. Malaise, gastrointestinal pain, dyspepsia and taste perversion were also reported.

**Nevirapine:**
The most clinically important adverse events associated with nevirapine therapy are rash and increases in liver function tests. Cases of hypersensitivity reactions have been observed.

The major clinical toxicity of nevirapine is rash, with nevirapine-attributable rash occurring in 16% of patients in combination regimens in Phase II/III controlled studies. Thirty-five percent of patients treated with nevirapine experienced rash compared with 19% of patients treated in control groups of either zidovudine + didanosine or zidovudine alone. Severe or life-threatening rash occurred in 6.6% of nevirapine-treated patients compared with 1.3% of patients treated in the control groups.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions; with or without pruritus, located on the trunk, face and extremities. The majority of severe rashes occurred within the first 28 days of treatment. 25% of the patients with severe rashes required hospitalization, and one patient required surgical intervention. Overall, 7% of patients discontinued nevirapine due to rash.

With respect to laboratory abnormalities, asymptomatic elevations in GGT levels are more frequent in nevirapine recipients than in controls. Because clinical hepatitis has been reported in nevirapine-treated patients, monitoring of ALT (SGPT) and AST (SGOT) is strongly recommended, especially during the first six months of nevirapine treatment (See Warnings and Precautions). Decreased neutrophils (< 750/mm3), platelets (< 50,000/mm3) and Hb (< 8.0 g/dL), and increased total bilirubin (> 2.5 mg/dL) have also been reported.