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

The following is based on Product Information for Triomune tablets and the WHO model formulary for each individual component.
Source: (http://mednet3.who.int/EMLib/modelFormulary/modelFormulary.asp).

Name:

Lamivudine,
PLUS
Stavudine
PLUS
Nevirapine used in the treatment of HIV infection.

Composition:

Tablets, containing 200mg nevirapine, 150mg lamivudine and 30mg stavudine or 200mg nevirapine, 150mg lamivudine and 40mg stavudine.

Use:

For the treatment for HIV-1 infection in adults. . Lamivudine and stavudine are Nucleotide/Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and nevirapine is a Non-Nucleotide/Nucleoside Reverse Transcriptase Inhibitors (NNRTI).

Dosage and administration:

Lamivudine plus stavudine plus nevirapine:
Treatment with the fixed combination should not be started on Day 1. For the first two weeks, your doctor will tell you to start therapy by taking nevirapine, lamivudine and stavudine separately, as follows: Take one 200 mg nevirapine tablet once daily for the first two weeks, whilst taking stavudine (30 or 40 mg depending on your body weight) and lamivudine (150 mg) twice daily. If during this period you experience no rash or other side effects, your doctor will instruct you to start therapy with the fixed dose combination.

Triomune (the fixed dose combination) should be taken by mouth twice daily, with or without food.

<u>Contraindications and precautions for use</u>:

Lamivudine plus stavudine plus nevirapine:

HYPERSENSITIVITY REACTION
Since Triomune contains nevirapine, some patients taking Triomune may develop a hypersensitivity reaction (a serious allergic reaction). **Patients may develop severe liver disease or skin reactions that may be life-threatening.** The risk of these reactions is greatest during the first 6 weeks of treatment. Your doctor should check you clinically and do liver function tests (blood tests) often in the first 6 weeks of therapy. These reactions can also occur later and checks for liver problems should continue regularly during your therapy. Patients with significant altered liver function tests and patients with clinical hepatitis B or C may have an increased chance of liver toxicity while taking nevirapine and should be carefully monitored. Patients with higher CD4 counts, particularly HIV+ women with CD4 cell counts $\geq 250/mm^3$ and HIV+ men with CD4 counts $\geq 400/mm^3$, seem to have a greater chance of developing a rash with associated liver damage while taking nevirapine, even in the absence of concomitant hepatic disease.

In rare cases liver problems have led to liver failure, which can lead to liver transplants or death. **Therefore, if you develop any of the following symptoms of liver problems, inform your doctor right away:**
- General ill feeling or "flu-like" symptoms
- Tiredness
- Nausea (feeling sick to your stomach)
- Lack of appetite
- Yellowing skin or whites of your eyes
- Dark urine
- Pale stools (bowel movements)
- Pain, ache, or sensitivity to touch on your right side below your ribs

Nevirapine can cause serious skin rash. 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 Triomune and inform your doctor right away**:
- General ill feeling or "flu-like" symptoms
- Fever
- Muscle or joint aches
- Tiredness
- Conjunctivitis (red or inflamed eyelids)
- Blisters
- Mouth sores
- Swelling of your face

If your doctor tells you to stop treatment with Triomune because you have these types of serious reactions, **never take Triomune again**.

Changes in body fat have been seen in some patients taking long term antiretroviral therapy, this is called lipodystrophy syndrome. These changes may include loss of fat from the legs, arms and face, increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk and increase in blood triglycerides and cholesterol levels may also happen. The cause and long-term health effects of these conditions are not well known at this time.

The class of medicines to which both stavudine and lamivudine belong (NRTIs) can cause a condition called lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. Lactic acidosis, if it occurs, usually develops after a few months of treatment. Deep, rapid breathing, drowsiness, and non-specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. This rare but serious side effect occurs more frequently in women, particularly if very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with Triomune, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

Stavudine can cause a neurological condition known as peripheral neuropathy. If this happens, the symptoms are numbness, tingling, or pain in the hands or feet and you should inform your doctor immediately. Neuropathy occurs with greatest frequency in patients with advanced HIV disease or in patients who have suffered from peripheral neuropathy in the past. If neuropathy develops, the dose of stavudine may need to be reduced, and therapy with Triomune may no longer be appropriate. Your doctor will advise you regarding this.

If you have hepatitis B infection, you should not stop your treatment without instructions from your doctor, as you may have a recurrence of your hepatitis. This recurrence may be more severe if you have serious liver disease.

Pregnancy
Inform your doctor if you are pregnant or planning to become pregnant. Triomune should be taken during pregnancy only after consultation with your doctor.

Breast feeding
Inform your doctor if you are breastfeeding. Some health experts recommend that HIV-infected women should not breastfeed their infants in order to avoid transmission of HIV.

Driving and using machines
No studies on the effects of Triomune on the ability to drive and use machines have been performed. However, you should take into account the state of your health and the possible side effects of Triomune before considering driving or using machines.

Taking Triomune with other medicines
Please inform your doctor if you are taking or have recently taken any other medicines, even those not prescribed. Triomune should not be taken with zidovudine, zalcitabine, ketoconazole, rifampin and clarithromycin. Triomune may interact with certain other medicines, which may make side effects worse. It is important that you tell your doctor if you are taking any of the following medicines (ask your doctor if you are not sure):

- trimethoprim/sulfamethoxazole
- efavirenz

- rifabutin
- fluconazole
- indinavir
- lopinavir/ritonavir
- warfarin
- ganciclovir
- foscarnet

Furthermore, nevirapine can reduce the efficacy of oral contraceptive pills. Hence, oral contraceptives should not be used as the sole method of contraception. An alternative or additional method of contraception is recommended.

If you are taking methadone, your doctor may need to adjust your methadone dose.

It is important that your doctor knows about all the medicines you are taking. Tell your doctor about all the medicines you are taking, including vitamin supplements, herbal remedies or homeopathic remedies including those you have bought yourself, as well as drugs not listed above.

Adverse effects:

Lamivudine plus stavudine plus nevirapine:

Serious side effects that may occur with the use of the fixed dose combination are:

- Lactic acidosis (severe increase of lactic acid in the blood), severe liver enlargement**,** including inflammation (pain and swelling) of liver and liver failure, which can cause death.

Symptoms of lactic acidosis may include:

- Nausea, vomiting, or unusual or unexpected stomach discomfort
- Feeling very weak and tired
- Shortness of breath
- Weakness in arms and legs

Inform your doctor immediately if you experience any of the following symptoms.

- Peripheral neuropathy, a nerve disorder of the hand and feet. This nerve disorder is rare, but may be serious. If you have numbness, tingling, burning, or pain in the feet and/or hands, inform your doctor immediately.
- Pancreatitis is a dangerous inflammation of the pancreas. It may cause death. Tell your doctor right away if you develop stomach pain, nausea or vomiting. These can be signs of pancreatitis.
- Loss of fat from the legs, arms and face.
- Severe, life-threatening, and in some cases fatal liver disease (hepatitis, liver failure) and skin reactions have been reported. In a small number of patients, rash has been severe and has resulted in death.

Combination antiretroviral therapy may also cause raised sugar in the blood, hyperlipidaemia (increased fats in the blood) and resistance to insulin.

Individual Components:

Lamivudine:
nausea, vomiting, diarrhoea, abdominal pain; cough; headache, fatigue, insomnia; malaise, fever, rash, alopecia, muscle disorders; nasal symptoms; peripheral neuropathy reported; rarely pancreatitis (discontinue); neutropenia, anaemia, thrombocytopenia and red-cell aplasia; lactic acidosis; raised liver enzymes and serum amylase reported.

Stavudine:
peripheral neuropathy (dose-related, see above); pancreatitis; nausea, vomiting, diarrhoea, constipation, anorexia, abdominal discomfort; chest pain; dyspnoea; headache, dizziness, insomnia, mood changes; abnormal dreams, cognitive dysfunction, drowsiness, depression, anxiety; gynaecomastia; asthenia, musculoskeletal pain; influenza-like symptoms, rash and other allergic reactions; lymphadenopathy; neoplasms; elevated liver enzymes and serum amylase; neutropenia, thrombocytopenia.

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.