SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg Dispersible Tablets*

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Lamivudine 30 mg / nevirapine 50 mg / zidovudine 60 mg

Excipients with known effects:

Each Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablet contains 62 mg of lactose monohydrate.

For a full list of excipients, see section 6.1

3. **PHARMACEUTICAL FORM**

Dispersible tablet

White to off-white circular biconvex tablets engraved “LNZ” on one side and a break line on the other side.

The tablet can be divided into equal doses.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected children weighing less than 25 kg.

This fixed combination replaces the three components (lamivudine, nevirapine and zidovudine) used separately in similar dosages. Treatment must be started with separate formulations of lamivudine, nevirapine and zidovudine at least for the first 2 weeks (see sections 4.2 and 4.4), until the patient is on the twice daily nevirapine maintenance.

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

*This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and lactation, to allow full access to all relevant information.*

4.2 **Posology and method of administration**

Oral use.

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

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
For situations where discontinuation or dose reduction of one of the components of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets, is necessary, separate preparations of lamivudine, nevirapine and zidovudine should be used.

Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is a fixed-dose combination, and cannot be used during the 2 week period of nevirapine lead-in therapy.

Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets may be taken with or without food.

**Children weighing less than 25 kg:**
The number of tablets by weight band to be taken twice daily (approximately 12 hours apart) is shown in the table below:

<table>
<thead>
<tr>
<th>Child’s weight</th>
<th>Number of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>morning</td>
</tr>
<tr>
<td>3 kg to less than 6 kg</td>
<td>1</td>
</tr>
<tr>
<td>6 kg to less than 10 kg</td>
<td>1.5</td>
</tr>
<tr>
<td>10 kg to less than 14 kg</td>
<td>2</td>
</tr>
<tr>
<td>14 kg to less than 20 kg</td>
<td>2.5</td>
</tr>
<tr>
<td>20 kg to less than 25 kg</td>
<td>3</td>
</tr>
</tbody>
</table>

The required number of tablets should be dispersed in approximately 10 ml of water and the entire amount should be swallowed. The mixture (tablets dispersed in water) should be used within 10 minutes. Children weighing 25 kg or more, adolescents and adults:

For these patient groups, other fixed dose formulations with higher amounts of the active substances (i.e. lamivudine 150 mg, nevirapine 200 mg and zidovudine 300 mg) are available.

**Dose adjustment**

*Patients with haematological adverse reactions*
Discontinuation of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets and substitution of zidovudine may need to be considered in patients whose haemoglobin level or neutrophil count falls to clinically significant levels (see sections 4.3 and 4.4).

**Renal Impairment**
Since different dose adjustments for zidovudine and lamivudine are recommended in patients with renal impairment (creatinine clearance ≤50 ml/min), separate preparations of lamivudine, nevirapine and zidovudine should be administered in this situation (see section 4.4).

**Hepatic impairment**
Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is contraindicated in patients with severe hepatic impairment (see section 4.3). In patients with moderate hepatic impairment dosage reductions may be necessary but, due to the large variability in zidovudine exposures, precise recommendations cannot be made. Physicians should closely monitor such patients for signs of zidovudine toxicity, and discontinuation of therapy with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets and dose interval adjustment or substitution for zidovudine may be necessary.

**Discontinuation and reintroduction of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets**
Special consideration should be given to the safe reintroduction of therapy with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets (see section 4.4). In patients having treatment with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets interrupted for more than 7 days, therapy should be reintroduced with separate formulations of lamivudine, nevirapine and zidovudine, with a dose escalation period with nevirapine once daily dosing for 14 days (at half the maintenance dose), followed by a twice daily regimen(see section 4.4).
4.3 Contraindications

Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets 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 C or ALT or AST values >5 times the upper limit of normal [ULN])
- History of severe rash, rash accompanied by constitutional symptoms or liver toxicity due to nevirapine
- Abnormally low neutrophil counts (less than 0.75 \( \times 10^9 \) /litre) or abnormally low haemoglobin level (less than 7.5 g/decilitre or 4.7 mmol/litre).

Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets must not be used concomitantly with rifampicin or herbal preparations containing St. John’s Wort (Hypericum perforatum) due to the risk of decreased plasma concentrations and reduced clinical effects of nevirapine (see section 4.5).

4.4 Special warnings and special precautions for use

The first 18 weeks of therapy with nevirapine are a critical period during which patients should be closely monitored for severe and life-threatening skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) and for serious and life-threatening hepatitis or hepatic failure. The risk of hepatic events and skin reactions is greatest in the first 6 weeks of therapy. Intensive clinical and laboratory monitoring, including liver function tests, should be performed when initiating therapy and during the first 6 weeks of treatment. However, the risk of hepatic events persists beyond this period and monitoring should continue at frequent intervals. Female gender and higher CD4 counts at the initiation of therapy increase the risk of hepatic adverse events. Unless the benefit outweighs the risk, nevirapine should not be initiated in women with CD4 cell count greater than 250 cells/mm\(^3\), in men with CD4 cell count greater than 400 cells/mm\(^3\) or in patient with unknown CD4 cell count.

Patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. Nevirapine must not be restarted following severe hepatic, skin or hypersensitivity reactions (see section 4.3). In some cases, hepatic injury has progressed despite discontinuation of treatment.

The dosage must be strictly adhered to, especially in the 14-day lead-in period (see section 4.2).

Dose adjustments

It is recommended that separate preparations of lamivudine, nevirapine and zidovudine be administered when any dosage adjustment is necessary (see section 4.2). 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 health care providers experienced in the treatment of HIV infection.

Transmission of HIV

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.
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 starting 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 in adults are female sex, higher baseline CD4 counts, higher baseline levels of alanine aminotransferase (ALT), 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. These risk factors may also apply to children.

Intensive clinical and laboratory monitoring, including liver function tests, should be performed when initiating therapy with nevirapine-containing products and during the first 6 weeks of treatment. 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. Any nevirapine-containing product, such as Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets, must be permanently discontinued in any patient experiencing severe liver toxicity (see section 4.3; asymptomatic GGT elevations are not a contraindication to continuing therapy).

Caution should be exercised when administering Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets 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 30mg/50mg/60mg dispersible tablets 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 who 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 (see section 4.3).

In patients with moderate to severe liver disease [Child-Pugh score 7-15; Class C] large variability in zidovudine exposures has been observed, therefore physicians should closely monitor these patients for signs of zidovudine toxicity (see section 4.2). Use of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is contraindicated in patients with severe hepatic impairment (see section 4.3). Cutaneous reactions

Patients should be closely monitored for cutaneous reactions during the first 18 weeks of treatment. Any patient who has severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise should discontinue nevirapine and immediately seek medical evaluation. In these patients nevirapine must not be restarted.

If patients present with a suspected nevirapine-associated rash, liver function tests should be performed. Patients with moderate to severe elevations (AST or ALT > 5 times ULN) should permanently discontinue nevirapine.

If a hypersensitivity reaction occurs, characterized by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement such as hepatitis, eosinophilia, granulocytopenia, and/or renal dysfunction, nevirapine must be permanently discontinued and not be re-introduced (see section 4.3).
The risk of developing serious cutaneous reactions is increased by failure to follow the initial dosing of 200 mg once daily during the lead-in period (see sections 4.1 and 4.2) or by delaying medical consultation after initial cutaneous symptoms. Exceeding the recommended dose of nevirapine might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Women may be at higher risk of developing rash, whether receiving nevirapine or non-nevirapine containing therapy.

Patients should be instructed that a major toxicity of nevirapine is rash. They should be advised to seek medical evaluation **without delay** if any rash occurs. The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. Patients should be instructed that the dose should not be increased if any rash occurs during the two-week lead-in dosing period, until the rash resolves. The 200 mg once-daily dosing regimen should not be continued beyond 28 days when an alternative treatment should be instituted.

**Starting and reintroducing nevirapine-containing preparations, such as Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets**

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 dispersible tablets 30mg/50mg/60mg for more than 7 days and is to be restarted later, therapy should be reintroduced with separate formulations of lamivudine, zidovudine and nevirapine, with a dose escalation period with nevirapine once daily dosing for 14 days, followed by the twice daily maintenance regimen. (see sections 4.1 and 4.2).

**Discontinuation of nevirapine-containing preparations, such as Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets**

Due to the long half-life of nevirapine, discontinuation of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets without immediate institution of another effective antiretroviral therapy, will lead to a period of de facto nevirapine monotherapy. Since nevirapine has a low barrier to resistance, this may lead to high-level nevirapine resistance (see section 5.1).

There is no validated strategy for handling this risk. However, covering the period of slow nevirapine elimination after discontinuation with 2-4 weeks of boosted protease inhibitor monotherapy, in case a new antiretroviral regimen is not immediately instituted, has been suggested.

**Haematological monitoring**

Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients receiving zidovudine. These occurred more frequently at higher zidovudine dosages (1200-1500mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease. Haematological parameters should therefore be carefully monitored (see section 4.3) in patients receiving Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets. These haematological effects are not usually observed before 4-6 weeks therapy. Therefore, it is recommended that haematological parameters be monitored periodically in patients receiving Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets, for example as follows:

- In advanced HIV disease: at least every two weeks during the first three months of zidovudine therapy, and monthly thereafter.
- In early (asymptomatic) 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 (see section 4.3), 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 nucleoside reverse transcriptase inhibitors (NRTI). Several other agents of this class are known to cause lactic acidosis. Preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, considered a putative class effect of nucleoside analogues, is very low for lamivudine. However, this risk cannot be excluded. Lactic acidosis may occur after a few to several months of NRTI treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity. Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk. 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 and lamivudine. Lactic acid levels > 10 mmol/l usually are a medical emergency.

Lipodystrophy and metabolic disorders
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV-infected patients. A higher risk of lipodystrophy has been associated with older age, 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 (see section 4.8).

Pancreatitis
Treatment with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

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) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convolution, 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 findings do not affect current national recommendations recommending use of antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome
In HIV-infected patients with pre-existing severe immune deficiency, within 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. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.
**Post-Exposure Prophylaxis**

Serious hepatotoxicity (including liver failure requiring transplantation, in one instance) has been reported in HIV-uninfected individuals receiving multiple doses of nevirapine in the setting of post-exposure prophylaxis (PEP), an unapproved use. Nevirapine-containing products should not be used for this purpose.

**Excipients**

Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.

Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

4.5 Interaction with other medicinal products and other forms of interaction

As Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets contains lamivudine, nevirapine and zidovudine, any interactions that have been identified with these agents individually may occur with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets.

Lamivudine undergoes limited metabolism and is almost completely eliminated via the kidneys. Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated metabolite, followed by renal excretion. Nevirapine is metabolised by CYP3A and by CYP2B6. Therefore any inducers/inhibitors of these metabolic pathways may alter plasma concentrations of nevirapine.

Neither lamivudine nor zidovudine inhibit the major cytochrome P450 isoforms, however nevirapine is an inducer of the hepatic cytochrome P450 enzymes, with maximal induction occurring within 2-4 weeks after initiating full dose therapy. Thus, 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 30mg/50mg/60mg dispersible tablets, especially when they have a small therapeutic margin.

Table of drug interactions for Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets

The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised (increased exposure is indicated as “↑”, decreased exposure as “↓”, no change as “↔”, thrice daily as t.i.d., twice daily as “b.i.d.”, and once daily as “q.d.”).

<table>
<thead>
<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine + nevirapine</td>
<td>Interaction not studied</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td></td>
<td>+ lamivudine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ zidovudine</td>
<td></td>
</tr>
<tr>
<td>Tenofovir + nevirapine</td>
<td>Interaction not studied</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td></td>
<td>+ lamivudine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ idovudine</td>
<td></td>
</tr>
</tbody>
</table>
## Interaction

### Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets

<table>
<thead>
<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir + nevirapine + lamivudine + zidovudine</td>
<td>Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets should not be co-administered with emtricitabine because of overlapping resistance and lack of additive antiretroviral effects</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine + lamivudine</td>
<td>Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets should not be co-administered with stavudine due to no additive effect in vivo, and antagonism in vitro</td>
<td></td>
</tr>
<tr>
<td>Stavudine + zidovudine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Non-nucleoside reverse transcriptase inhibitors (NNRTI)

<table>
<thead>
<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz, Etravirine, Delavirdine, Rilpivirine + nevirapine</td>
<td>Co-administration of an NNRTI and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is not recommended because of additive toxicity and no benefit in efficacy</td>
<td></td>
</tr>
</tbody>
</table>

### Protease inhibitors

<table>
<thead>
<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/ritonavir 300/100 mg once daily</td>
<td>Co-administration of atazanavir, with or without ritonavir, and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is not recommended</td>
<td></td>
</tr>
</tbody>
</table>
| 400/100 mg once daily + nevirapine | Atazanavir/ritonavir 300/100 mg:  
Atazanavir/ritonavir AUC ↓ 0.58 (0.48–0.71)  
Atazanavir/ritonavir C_{min} ↓ 0.28 (0.20–0.40)  
Atazanavir/ritonavir C_{max} ↓ 0.72 (0.60–0.86)  
Atazanavir/ritonavir 400/100 mg:  
Atazanavir/r AUC ↓ 0.81 (0.65–1.02)  
Atazanavir/ritonavir C_{min} ↓ 0.41 (0.27–0.60)  
Atazanavir/ritonavir C_{max} ↔ 1.02 (0.85–1.24) (compared to 300/100 mg without nevirapine)  
Nevirapine AUC ↑ 1.25 (1.17–1.34)  
Nevirapine C_{min} ↑ 1.32 |  |
<table>
<thead>
<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1.22–1.43) Nevirapine C&lt;sub&gt;max&lt;/sub&gt; ↑ 1.17 (1.09–1.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atazanavir: AUC: ↓ 25% (↓ 42 to ↓ 3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;: ↓ 28% (↓ 50 to ↑ 5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;min&lt;/sub&gt;: ↓ 26% (↓ 46 to ↑ 10)</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir 400/100 mg bid + nevirapine</td>
<td>No significant interaction</td>
<td>Darunavir and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets can be co-administered without dose adjustments.</td>
</tr>
<tr>
<td>Fosamprenavir 1.4 g bid + nevirapine</td>
<td>Amprenavir AUC ↓ 0.67 (0.55–0.80) Amprenavir C&lt;sub&gt;min&lt;/sub&gt; ↓ 0.65 (0.49–0.85) Amprenavir C&lt;sub&gt;max&lt;/sub&gt; ↓ 0.75 (0.63–0.89)</td>
<td>Co-administration of fosamprenavir and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is not recommended, if fosamprenavir is not co-administered with ritonavir.</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir (700/100 mg bid) + nevirapine + lamivudine + zidovudine</td>
<td>Amprenavir AUC ↔ 0.89 (0.77–1.03) Amprenavir C&lt;sub&gt;min&lt;/sub&gt; ↓ 0.81 (0.69–0.96) Amprenavir C&lt;sub&gt;max&lt;/sub&gt; ↔ 0.97 (0.85–1.10)</td>
<td>Fosamprenavir/ritonavir and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets can be co-administered without dose adjustments</td>
</tr>
<tr>
<td>Indinavir (800 mg q8h) + nevirapine</td>
<td>indinavir: AUC ↓ mean 31%, C&lt;sub&gt;min&lt;/sub&gt; ↓ mean 44% nevirapine: ↔</td>
<td>Concomitant treatment of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets with unboosted indinavir is not recommended. Concomitant treatment with ritonavir-boosted indinavir is recommended only if</td>
</tr>
</tbody>
</table>
## Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir (400/100 mg capsules bid) + nevirapine</td>
<td>Adults: Lopinavir AUC ↓ 0.73 (0.53–0.98) Lopinavir C&lt;sub&gt;min&lt;/sub&gt; ↓ 0.54 (0.28–0.74) Lopinavir C&lt;sub&gt;max&lt;/sub&gt; ↓ 0.81 (0.62–0.95) In adults, an increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) or 500/125 mg (5 tablets with 100/25 mg each) twice daily with food is recommended For dosing in children when coadministering nevirapine, see lopinavir/ritonavir product information.</td>
</tr>
<tr>
<td>Ritonavir (600 mg bid) + nevirapine + lamivudine + zidovudine</td>
<td>no interaction</td>
</tr>
<tr>
<td>Saquinavir/ritonavir + nevirapine</td>
<td>The limited data available with saquinavir soft gel capsule boosted with ritonavir do not suggest any clinically relevant interaction between saquinavir boosted with ritonavir and nevirapine Saquinavir/ritonavir and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets can be co-administered without dose adjustments.</td>
</tr>
<tr>
<td>Tipranavir/ritonavir 500/200 mg bid + nevirapine</td>
<td>Nevirapine: AUC ↓ 0-25% Both tipranavir and nevirapine are hepatotoxic. Co-administration of tipranavir and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is not recommended.</td>
</tr>
</tbody>
</table>

## Entry inhibitors

| Enfuvirtide + nevirapine | Due to the metabolic pathway no clinically significant pharmacokinetic interactions are expected between enfuvirtide and nevirapine. Enfuvirtide and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets can be co-administered without dose adjustments. |
| Maraviroc 300 mg qd + nevirapine | Maraviroc AUC ↔ 1.01 (0.6–1.55) Maraviroc C<sub>min</sub> ND Maraviroc C<sub>max</sub> ↔ 1.54 (0.94–2.52) compared to historical controls Nevirapine concentrations not measured, no effect is Maraviroc and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets can be co-administered without dose adjustments. |
### Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integrase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Raltegravir 400 mg bid + nevirapine</td>
<td>No clinical data available. Due to the metabolic pathway of raltegravir no clinically relevant interaction is expected.</td>
</tr>
<tr>
<td>Elvitegravir/ cobicistat + nevirapine</td>
<td>Interaction has not been studied. Cobicistat, a cytochrome P450 3A inhibitor significantly inhibits hepatic enzymes, as well as other metabolic pathways. Therefore coadministration would likely result in altered plasma levels of cobicistat and nevirapine.</td>
</tr>
</tbody>
</table>

*Antivirals for Chronic Hepatitis Band C*
<table>
<thead>
<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir + nevirapine</td>
<td>Boceprevir is partly metabolized by CYP3A4/5. Co-administration of boceprevir with medicines that induce or inhibit CYP3A4/5 could increase or decrease exposure. Plasma trough concentrations of boceprevir were decreased when administered with an NNRTI with a similar metabolic pathway as nevirapine. The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed.</td>
<td>It is not recommended to co-administer boceprevir and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets.</td>
</tr>
<tr>
<td>Adefovir + nevirapine</td>
<td>Results of in vitro studies showed a weak antagonism of nevirapine by adefovir (see section 5.1), this has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not influence any of the common CYP isoforms known to be involved in human drug metabolism and is excreted renally. No clinically relevant drug-drug interaction is expected.</td>
<td>Adefovir and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets may be coadministered without dose adjustments.</td>
</tr>
<tr>
<td>Entecavir + nevirapine</td>
<td>Entecavir is not a substrate, inducer or an inhibitor of cytochrome P450 (CYP450) enzymes. Due to the metabolic pathway of entecavir, no clinically relevant drug-drug interaction is expected.</td>
<td>Entecavir and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets may be coadministered without dose adjustments.</td>
</tr>
<tr>
<td>Drugs by Therapeutic Area</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Interferons (pegylated interferons alfa 2a and alfa 2b) + nevirapine</td>
<td>Interferons have no known effect on CYP 3A4 or 2B6. No clinically relevant drug-drug interaction is expected.</td>
<td>Interferons and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets may be co-administered without dose adjustments</td>
</tr>
<tr>
<td>Ribavirin+ zidovudine</td>
<td>Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the HIV regimen, therefore the combination of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets and ribavirin should be avoided, if possible.</td>
<td></td>
</tr>
</tbody>
</table>
### Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir + nevirapine</td>
<td>Telaprevir is metabolised in the liver by CYP3A and is a P-glycoprotein substrate. Other enzymes may be involved in the metabolism. Co-administration of telaprevir and medicinal products that induce CYP3A and/or P-gp may decrease telaprevir plasma concentrations. No drug-drug interaction study of telaprevir with nevirapine has been conducted, however, interaction studies of telaprevir with an NNRTI with a similar metabolic pathway as nevirapine demonstrated reduced levels of both. Results of DDI studies of telaprevir with efavirenz indicate that caution should be exercised when co-administering telaprevir with P450 inducers. Caution should be exercised when co-administering telaprevir with nevirapine. If co-administered with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets, an adjustment in the telaprevir dose should be considered.</td>
</tr>
<tr>
<td>Simeprevir + nevirapine</td>
<td>Not studied. Altered plasma concentrations of simeprevir are expected. (CYP3A4 enzyme induction) It is not recommended to co-administer Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets with simeprevir.</td>
</tr>
<tr>
<td>Daclatasvir + nevirapine</td>
<td>Interaction not studied. Expected due to CYP3A4 induction by nevirapine: ↓ Daclatasvir Due to the lack of data, Co-administration of daclatasvir and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is not recommended.</td>
</tr>
</tbody>
</table>

### Antibacterials/Antituberculosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin 500 mg bid + nevirapine</td>
<td>Clarithromycin AUC ↓ 0.69 (0.62–0.76) Clarithromycin C&lt;sub&gt;min&lt;/sub&gt; ↓ 0.44 (0.30–0.64) Clarithromycin C&lt;sub&gt;max&lt;/sub&gt; ↓ 0.77 (0.69–0.86)</td>
<td>Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against <em>Mycobacterium avium-intracellulare complex</em> overall activity against the pathogen may be compromised.</td>
</tr>
<tr>
<td>Drugs by Therapeutic Area</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16–1.73)</td>
<td>be altered. Alternatives to clarithromycin, such as azithromycin should be considered when co-treating with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets. Close monitoring for hepatic abnormalities is recommended</td>
<td></td>
</tr>
<tr>
<td>Metabolite 14-OH clarithromycin C&lt;sub&gt;min&lt;/sub&gt; ↔ 0 (0.68–1.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolite 14-OH clarithromycin C&lt;sub&gt;max&lt;/sub&gt; ↑ 1.47 (1.21–1.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine AUC ↑ 1.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine C&lt;sub&gt;min&lt;/sub&gt; ↑ 1.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine C&lt;sub&gt;max&lt;/sub&gt; ↑ 1.24 compared to historical controls.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin 500mg bid + Zidovudine 100mg every 4 hours</td>
<td>Zidovudine AUC ↓ 12%</td>
<td>Separate administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets and clarithromycin by at least 2 hours is recommended</td>
</tr>
<tr>
<td>Rifabutin 150 or 300 mg qd + nevirapine</td>
<td>Rifabutin AUC ↑ 1.17 (0.98–1.40)</td>
<td>Rifabutin and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets can be co-administered without dose adjustments. However, due to high intersubject variability 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.</td>
</tr>
<tr>
<td>Rifabutin C&lt;sub&gt;min&lt;/sub&gt; ↔ 1.07 (0.84–1.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin C&lt;sub&gt;max&lt;/sub&gt; ↑ 1.28 (1.09–1.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolite 25-O-desacetylrifabutin AUC ↑ 1.24 (0.84–1.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolite 25-O-desacetylrifabutin C&lt;sub&gt;min&lt;/sub&gt; ↑ 1.22 (0.86–1.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolite 25-O-desacetylrifabutin C&lt;sub&gt;max&lt;/sub&gt; ↑ 1.29 (0.98–1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical data was reported.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin 600 mg qd + nevirapine</td>
<td>Rifampicin AUC ↔ 1.11 (0.96–1.28)</td>
<td>Co-administration of rifampicin and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is not recommended. When treating tuberculosis, substituting an alternative</td>
</tr>
<tr>
<td>Rifampicin C&lt;sub&gt;min&lt;/sub&gt; ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin C&lt;sub&gt;max&lt;/sub&gt; ↔ 1.06 (0.91–1.22)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trimethoprim/sulfamethoxazole (Co-trimoxazole) 160mg/800mg td for 5 days + lamivudine 300mg single dose</strong></td>
<td>antiretroviral drug combination for Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets, or substituting rifabutin for rifampicin should be considered.</td>
</tr>
<tr>
<td>Nevirapine $C_{\text{max}} \downarrow 0.32$ Nevirapine $C_{\text{min}} \downarrow 0.50$ compared to historical controls.</td>
<td>No dosage adjustment is necessary when Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is co-administered with trimethoprim/sulfamethoxazole, unless patient has renal impairment (see section 4.2). When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim/sulfamethoxazole for the treatment of pneumocystis jirovecii pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided.</td>
</tr>
</tbody>
</table>

### Antifungals

<table>
<thead>
<tr>
<th>Fluconazole 200mg q.d + nevirapine +zidovudine</th>
<th>Fluconazole 200mg once daily Fluconazole AUC $\leftrightarrow 0.94$ (0.88–1.01) Fluconazole $C_{\text{min}} \leftrightarrow 0.93$ (0.86–1.01) Fluconazole $C_{\text{max}} \leftrightarrow 0.92$ (0.85–0.99) Nevirapine: exposure: $\uparrow 100%$ compared with historical data where nevirapine was administered alone. zidovudine: AUC $\uparrow 74%$</th>
<th>When Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is given concurrently with fluconazole, patients should be monitored closely for signs of nevirapine and/or zidovudine toxicity.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole 200 mg q.d + nevirapine</td>
<td>Itraconazole AUC $\downarrow 0.39$ Itraconazole $C_{\text{min}} \downarrow 0.13$ Itraconazole $C_{\text{max}} \downarrow 0.62$ Nevirapine: there was no significant difference in nevirapine</td>
<td>A dose increase for itraconazole should be considered when Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is administered concomitantly.</td>
</tr>
</tbody>
</table>
### Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole 400 mg q.d + nevirapine</td>
<td>Co-administration of ketoconazole and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets is not recommended.</td>
</tr>
</tbody>
</table>

**Antimalarials**

| Atovaquone, chloroquine, mefloquine, proguanil, sulfadoxine or pyrimethamine + nevirapine | No formal interaction study available. | On theoretical basis, clinically significant interactions with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets are unlikely. |
| Atovaquone (750mg tid with food) + Zidovudine (200mg tid) | Atovaquone AUC ↔ Zidovudine AUC ↑ 33% | |
| Quinine + nevirapine | Quinine AUC ↓ 0.67 Quinine C<sub>max</sub> ↓ 0.64 | Quinine is extensively metabolised by CYP3A. Co-administration with nevirapine-containing products, such as Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets may decrease quinine exposure, and reduce the antimalarial effect. If available, other antimalarial treatment options should be used in patients treated with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets. |
| Amodiaquine/artesunate + 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. |
| Lumefantrine + nevirapine | Lumefantrine AUC ↑ 1.56 Lumefantrine C<sub>max</sub> ↑ 1.24 | Preliminary studies suggest no increase in adverse effects of lumefantrine. Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets and artemether + lumefantrine can be co-administered without dose adjustment (see also under... |
**Drugs by Therapeutic Area**

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration of Lamivudine/ Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin or its derivatives)</td>
<td>Halofantrine is metabolised by CYP3A; hence, co-treatment with nevirapine may decrease exposure. Co-treatment of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets with these agents is not recommended.</td>
</tr>
</tbody>
</table>

**Anticonvulsants**

| Carbamazepine, phenobarbital or phenytoin + nevirapine | No formal interaction study available. Concentrations of nevirapine and of the anticonvulsant are expected to be reduced, which might cause treatment failure. | Co-administration of carbamazepine, phenobarbital or phenytoin and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets should be avoided unless antiretroviral (and antiepileptic) effect can be monitored closely. |

| Valproic acid + nevirapine | No formal interaction study available | If coadministered with Lamivudine/ Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets monitor plasma concentrations of valproic acid. |

**Antacids**

| Cimetidine + nevirapine | Cimetidine: no significant effect on cimetidine pharmacokinetic parameters is seen. Nevirapine $C_{min}$ ↑ 1.07 | Cimetidine and Lamivudine/ Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets can be co-administered without dose adjustments. |

**Antithrombotics**

| Warfarin + nevirapine | The interaction between nevirapine and the antithrombotic agent warfarin is complex, with the potential for both increases and decreases in coagulation time when used concomitantly. | 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 30mg/50mg/60mg dispersible tablets. |

**Contraceptives**

| Depot medroxyprogesterone acetate (DMPA) 150 mg every 3 months + nevirapine | Depot medroxyprogesterone acetate $\text{AUC} \leftrightarrow$ Depot medroxyprogesterone acetate $C_{min} \leftrightarrow$ Depot medroxyprogesterone acetate $C_{max} \leftrightarrow$ | Nevirapine did not alter the ovulation suppression effects of depot medroxyprogesterone acetate. Depot medroxyprogesterone acetate and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets can be co-administered without dose adjustments. |
### Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nevirapine</strong> AUC ↑ 1.20 Nevirapine C&lt;sub&gt;max&lt;/sub&gt; ↑ 1.20</td>
<td>Ethinylestradiol 35 micrograms + nevirapine</td>
</tr>
<tr>
<td>Ethinylestradiol AUC ↓ 0.80 (0.67–0.97) Ethinylestradiol C&lt;sub&gt;min&lt;/sub&gt; ND Ethinylestradiol C&lt;sub&gt;max&lt;/sub&gt; ↔ 0.94 (0.79–1.12)</td>
<td>Oral hormonal contraceptives should not be used as the sole method of contraception in women taking Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets. Appropriate doses for hormonal contraceptives (oral or other forms of application) other than DMPA in combination with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets have not been established with respect to safety and efficacy.</td>
</tr>
<tr>
<td><strong>Ethinylestradiol/norethindrone</strong> (EE 0.35 mg/NET 1.0 mg, single dose + nevirapine) EE: AUC ↓ mean 20% NET: AUC ↓ mean 19% C&lt;sub&gt;max&lt;/sub&gt; ↓ mean 16%</td>
<td>Norethisterone 1 mg q.d + nevirapine Norethisterone AUC ↓ 0.81 (0.70–0.93) Norethisterone C&lt;sub&gt;min&lt;/sub&gt; ND Norethisterone C&lt;sub&gt;max&lt;/sub&gt; ↓ 0.84 (0.73–0.97)</td>
</tr>
<tr>
<td><strong>Cytotoxics</strong></td>
<td>Cytotoxics Cladribine + Lamivudine Interaction not studied In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine Concomitant use of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets with cladribine is not recommended.</td>
</tr>
<tr>
<td><strong>Opiate substitution</strong> Methadone Individual Patient Dosing + nevirapine Methadone 30-90mg td + Zidovudine 200mg every 4hours</td>
<td>Methadone AUC ↓ 0.40 (0.31–0.51) Methadone C&lt;sub&gt;min&lt;/sub&gt; ND Methadone C&lt;sub&gt;max&lt;/sub&gt; ↓ 0.58 (0.50–0.67) Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of narcotic withdrawal symptoms and methadone dose should be adjusted accordingly. Methadone-maintained patients beginning zidovudine therapy should be monitored for signs of zidovudine toxicity. No dose alteration of Zidovudine</td>
</tr>
<tr>
<td>Drugs by Therapeutic Area</td>
<td>Interaction</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Herbal Products**

| St. John’s Wort + nevirapine | Serum levels of nevirapine can be reduced by concomitant use of the herbal preparation St. John’s Wort (*Hypericum perforatum*). This is due to induction of drug metabolism enzymes and/or transport proteins by St. John’s Wort. | St. John’s Wort and Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets must not be co-administered (see section 4.3). The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John’s Wort. |

**Others**

| Doxorubicin + zidovudine | Concomitant use of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets and doxorubicin should be undertaken with caution due to possibly additive haematotoxicity. |
4.6 Pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should generally not rely on oral contraceptives as the sole method for birth control; since nevirapine might lower the plasma concentrations of hormonal contraceptives (see section 4.5).

Pregnancy

A moderate to large amount of data on pregnant women (300 to > 1000 pregnancies) indicate no malformations or foetal/neonatal toxicity associated with lamivudine, zidovudine or nevirapine. Animal studies on lamivudine, zidovudine and nevirapine do not indicate reproductive toxicity. For further information refer to: www.apregistry.com.

Breast-feeding

Lamivudine, zidovudine and nevirapine are found in breast milk of lactating mothers. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility

In reproductive toxicology studies with nevirapine, evidence of impaired fertility was seen in female rats. Neither lamivudine nor zidovudine had any effect on fertility in nonclinical studies (see section 5.3).

There are no data on the effect of zidovudine on human female fertility. In men, zidovudine has not been shown to affect sperm count, morphology or motility.

There are no data on the effect of lamivudine and nevirapine on human fertility.

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. However, dizziness may occur during treatment with Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

As Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets contains lamivudine, nevirapine and zidovudine, 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 serious adverse reactions (related to nevirapine) are Stevens-Johnson syndrome/toxic epidermal necrolysis, serious hepatitis/hepatic failure, and drug reaction with eosinophilia and systemic symptoms, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction. Rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with nevirapine use. The first 18 weeks of treatment is a critical period which requires close monitoring (see section 4.4).

The following list of side effects is mainly based on data from adult patients.

The most frequently reported adverse reactions are rash, headache, nausea, diarrhea, abdominal pain and myalgia. The most common serious adverse reactions include anaemia (which may require
transfusions), neutropenia, leucopenia, hypersensitivity reactions, and hepatic toxicity (see section 4.4).

The following adverse events have been reported in controlled clinical trials during treatment of HIV-1 infection with lamivudine, nevirapine and zidovudine. The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) or very rare (≤1/10,000). In addition, adverse events identified during post-approval use are listed. For some of them, estimates of frequency cannot be made (frequency category: ‘not known’), since they were reported voluntarily from a population of unknown size. These events have been included for the potential causal connection to lamivudine and/or nevirapine and/or zidovudine, 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
Not known: 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
Not known: Immune reconstitution syndrome (see section 4.4).

Investigations

Common: liver function test abnormal (alanine aminotransferase increased; transaminases increased;
aspartate aminotransferase increased; gamma-glutamyltransferase increased; hepatic enzyme
increased; hypertransaminasaemia)

Uncommon: blood phosphorus decreased; blood pressure increased

See also sections 4.4 and 4.5.

4.9 Overdose

Symptoms
There is limited experience of overdosage with lamivudine/nevirapine/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.

Treatment
There is no known antidote for any of the three agents. If overdose occurs, patients should be
monitored for toxicity (see section 4.8), and standard supportive treatment applied as necessary.
Because a negligible amount of lamivudine was removed via (4-hour) haemodialysis, continuous
ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous
haemodialysis would provide clinical benefit in a lamivudine overdose event.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations.
ATC code: J05AR05
Mechanism of action and pharmacodynamic effects
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-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. No antagonistic effects in vitro were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine and nevirapine). No antagonistic effects in vitro were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine and interferon-alpha).

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. In vitro nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates or HIV-2 isolates.

Clinical efficacy
In clinical trials in adults, 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. In a clinical trial in children in South Africa, 123 HIV-1 infected treatment-naïve patients between 3 months and 16 years of age received combination treatment with lamivudine, zidovudine and nevirapine for 48 weeks. Overall, 50% of paediatric patients achieved plasma HIV RNA <400 copies/ml at 48 Weeks.

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. M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility). In vitro data tend to suggest that the continuation of lamivudine in anti-retroviral regimens despite the development of M184V might provide residual anti-retroviral 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 analogue 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 NRTI class, 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 NNRTI therapy (see section 4.4).

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 30mg/50mg/60mg dispersible tablets in healthy adult volunteers, the following pharmacokinetic values were obtained:

<table>
<thead>
<tr>
<th>Pk parameter</th>
<th>Lamivudine [arithm. Mean (+SD)]</th>
<th>Zidovudine [arithm. Mean (+SD)]</th>
<th>Nevirapine [arithm. Mean (+SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_0-t (ng.h/ml)</td>
<td>5221 ± 1177</td>
<td>2359 ± 700</td>
<td>107690 ± 14271†</td>
</tr>
<tr>
<td>C_max (ng/ml)</td>
<td>1404 ± 456</td>
<td>2603 ± 1014</td>
<td>2684 ± 393</td>
</tr>
<tr>
<td>T_max (h)</td>
<td>0.92 ± 0.56</td>
<td>0.34 ± 0.19</td>
<td>1.85 ± 1.05</td>
</tr>
</tbody>
</table>

†AUC_0-72h

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 Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets.

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. Nevirapine is extensively biotransformed primarily via the cytochrome P450 isoymes 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, 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 be 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 be 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 a 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 by the kidneys and about 10% in faeces.

Pharmacokinetics in pregnancy
The pharmacokinetics of lamivudine and zidovudine during pregnancy were similar to that of non-pregnant women. Nevirapine clearance has been shown to be increased in pregnant women resulting in lower AUC and Cmax levels compared to non-pregnant women. The clinical relevance of this finding is unknown.

Pharmacokinetics in children
A clinical trial in 123 treatment-naïve, HIV-1-infected children in South Africa, aged 3 months to 16 years, examined the pharmacokinetics of nevirapine when administered in combination with zidovudine and lamivudine. The results indicated that using either the weight-based or the body surface area-based dosing resulted in nevirapine plasma concentrations which were comparable to those observed in adults.

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 foetuses 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 appeared to cause an increase in early embryonic deaths in rabbits at relatively low systemic exposures, comparable to those achieved in man, but not in the rat at very high systemic exposures. 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. Neither lamivudine nor zidovudine had any effect on fertility in nonclinical studies.

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
Sodium starch glycolate
Sucralose
Povidone
Colloidal silicon dioxide
Magnesium stearate
Flavour strawberry

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 30°C. Protect from light and moisture.

6.5 Nature and contents of container
White opaque HDPE bottle with white opaque polypropylene child resistant cap with induction seal liner. Pack size: 60 tablets.

White opaque HDPE bottle with white opaque HDPE screw closure with induction sealing liner. Pack size: 60 tablets.

6.6 Instructions for use and handling and disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER
Strides Arcolab Limited
Strides House, Bilekahalli
Bannerghatta Road
Bangalore – 560 076
India.
Tel: +91-80-67840738/739
Fax: +91-80-67840200
Email: info@stridesshasun.com

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)
HA 557
9. **DATE OF FIRST PREQUALIFICATION/RENEWAL OF PREQUALIFICATION**

24 October 2014

10. **DATE OF REVISION OF THE TEXT**

April 2016

**Reference list:**

General reference sources for this SmPC include:


Further references relevant to sections of the SmPC include:

**Section 4.2**

On intake with or without food

On dose adjustment in renal impairment

**Section 4.4**

On the hepatotoxicity of nevirapine
Martinez E et al. AIDS 2001; 15: 1261-8
Gonzalez de Requena D. et al. AIDS 2002; 16: 290-1
Sanne I et al. J Infect Dis 199; 179: 1116-23

On nevirapine-associated rash
Wit FW. et al. AIDS 2001; 15: 2423-9

On treatment discontinuation of nevirapine-containing products

On lactic acidosis
Carr A. Clin Infect Dis 2003; 36 (Suppl.2): S96-S100
On lipodystrophy
On post-exposure prophylaxis

Section 4.5
On specific drug interactions with lamivudine
van Leeuwen R et al. AIDS 1992; 6, 1471-5
On specific drug interactions with zidovudine
On specific drug interactions with nevirapine
Murphy RL et al. J Infect Dis 1999; 179: 1116-23

Section 4.6
On pregnancy
On nursing
Shapiro RL et al. J Infect Dis 2005; 192, 720-7
WHO Rapid Advice: HIV and infant feeding. November 2009:

Section 4.8
Gallant JE et al. JAMA 2004; 292: 191-201
Martin-Carbonero L et al. HIV Clin Trials 2003; 4: 115-20
Squires KE et al. AIDS 2000; 14: 1591-600
Eron J Jr et al. AIDS 2000; 14: 1601-10
Boubaker K et al. Clin Infect Dis 2001; 33: 1931-7
Fong IW et al. Lancet 1994; 344:1702

Section 5.1
On pharmacodynamic properties
Moyle GJ, Gazzard BG. Expert Opin Investig Drugs 1997; 6:191-200
On the clinical efficacy of zidovudine + lamivudine + nevirapine
FDA Clinical Pharmacology review:

On resistance
Castagna A et al. AIDS 2006; 20: 795
http://www.hivdb.stanford.edu
Sungkanuparph S. Clin Inf Dis 2007; 44: 447-52 Lamivudine/Zidovudine/Nevirapine WHOPAR part 4 05/2008,

Section 5.2
On the pharmacokinetics of zidovudine and lamivudine
Anderson PL. AIDS 2003; 17: 2159-68
On the pharmacokinetics of nevirapine
Penzak SR et al. HIV Med 2007; 8: 86-91
On the pharmacokinetics in children
FDA Clinical Pharmacology review: