SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Lamivudine USP ..... 150 mg
Zidovudine USP ..... 300 mg
For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg tablets are white coloured, film coated, oblong, biconvex tablets with 'DVR' embossed on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg is indicated in combination with another antiretroviral agent for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children weighing at least 25 kg.

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

4.2 Posology and method of administration

Oral use.

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

Patients weighing at least 25 kg

One tablet twice daily.
Tablets may be taken with food or between meals, swallowed with some water or another drink.

If the tablets cannot be swallowed whole, they may be crushed and combined with a small amount of semi- solid food or drink, and the whole dose taken immediately.

Patients weighing less than 25 kg

For these patients other formulations enabling administration of lower amounts of lamivudine and zidovudine are available (e.g. divisible tablets, tablets containing less active substances or liquid formulations).

Elderly

Special care is advised in the elderly because of age-associated changes such as decrease in renal function and alteration of haematological parameters.

Dose adjustments

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

Renal impairment

Since dose adjustment may be necessary in patients with renal impairment (creatinine clearance ≤ 50 ml/minute), it is recommended that separate preparations of lamivudine and zidovudine be administered (see section 4.4).

Hepatic impairment

No dose adjustment is necessary for mild to moderate hepatic impairment.
In patients with severe hepatic impairment, dose adjustment for zidovudine may be necessary. Therefore, it is recommended that separate preparations of lamivudine and zidovudine be administered in these patients (see section 4.4).

Haematological adverse reactions

Since substitution or dose reduction of zidovudine should be considered in patients whose haemoglobin concentrations or neutrophil counts fall to clinically significant levels, it is recommended that separate preparations of lamivudine and (if appropriate) zidovudine be administered (see section 4.4).

Missed dose

If a dose is missed it should be taken as soon as it is noted. If the next dose is due in less than 6 hours, the forgotten dose should be skipped and the next regular dose should be taken when it is due. No double dose should be taken to make up for missed doses.

4.3 Contraindications

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg is contraindicated in patients with:

- Hypersensitivity to lamivudine, zidovudine or to any excipient in the formulation,
- Abnormally low neutrophil count (< 0.75 x 10^9 /litre) (see section 4.4),
- Abnormally low haemoglobin (< 7.5 g/dl or 4.65 mmol/litre) (see section 4.4).

4.4 Special warnings and special precautions for use

Lamivudine and zidovudine should only be used with abacavir in the treatment of antiretroviral-naïve patients when a regimen based on a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) cannot be used. Concomitant use of stavudine with zidovudine should be avoided (see section 4.5).

Dose adjustment

It is recommended that separate preparations of lamivudine 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 for each of the products.

Opportunistic infections

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

Transmission of HIV

Patients should be advised that current antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions should continue to be taken to prevent transmission.

Haematological adverse reactions

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

Therefore, monitoring of haematological parameters is recommended in patients receiving Lamivudine and Zidovudine Tablets 150 mg/ 300 mg, e.g. as follows:

- In advanced HIV disease: at least every 2 weeks during the first 3 months of therapy, and monthly thereafter.
- In early (non-symptomatic) HIV disease, at a frequency depending on the overall condition of the patient: e.g. every 1–3 months.

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

Pancreatitis

Treatment with Lamivudine and Zidovudine Tablets 150 mg/ 300 mg should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Lactic acidosis

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

Mitochondrial dysfunction

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

Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. A higher risk of lipodystrophy has been associated with, for example, 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).

Immune Reactivation Syndrome

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

Liver disease

Caution should be exercised when administering Lamivudine and Zidovudine Tablets 150 mg/ 300 mg to any patient with chronic hepatitis B infection. Lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication and discontinuation of lamivudine or virological failure after development of resistance to lamivudine by HBV may cause hepatic deterioration and a hepatitis flare. If Lamivudine and Zidovudine Tablets 150 mg/ 300 mg is discontinued in a patient with HBV infection, the patient should be periodically monitored, both clinically and by assessment of liver function tests (ALT and bilirubin levels) and markers of HBV replication, for at least 4 months, and then as clinically indicated.

Patients with chronic hepatitis B or C who are treated with combination antiretroviral therapy, have an increased risk of severe and potentially fatal hepatic adverse events.
Patients with liver dysfunction have an increased risk of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If liver disease worsens in such patients, interruption or discontinuation of therapy should be considered.

Osteonecrosis

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

4.5 Interaction with other medicinal products and other forms of interaction

As Lamivudine and Zidovudine Tablets 150 mg/ 300 mg contains lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur.
Whereas lamivudine undergoes limited metabolism and is almost completely eliminated via the kidneys, zidovudine is primarily eliminated by hepatic conjugation, to form an inactive glucuronide metabolite. The following list of interactions is not exhaustive, but is representative of the classes of medicinal products where caution should be exercised.
Lamivudine and zidovudine are not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) and do not inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P450 enzymes.

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

Drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation concerning co-administration
Antiretrovirals		
Emtricitabine/Lamivudine	Overlapping resistance and lack of additive antiretroviral effects.	Emtricitabine should not be co- administered with Lamivudine and Zidovudine Tablets 150 mg/ 300 mg
Stavudine/Zidovudine	*In vitro* antagonism of anti-HIV activity between stavudine and zidovudine could result in decreased efficacy of both drugs.	Concomitant use of stavudine with Lamivudine and Zidovudine Tablets 150 mg/ 300 mg not recommended.
Anti-infectives		
Clarithromycin/Zidovudine (500 mg twice daily/100 mg every 4 hours)	Zidovudine AUC ↓12%	Administration of Lamivudine and Zidovudine Tablets 150 mg/ 300 mg and clarithromycin should be separated by at least 2 hours.

Drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation concerning co-administration
Rifampicin/Zidovudine (600 mg once daily/200 mg three times daily)	Zidovudine AUC ↓48% (UGT induction)	Insufficient data to recommend dosage adjustment.
Trimethoprim + sulfamethoxazole/ Lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (Organic cation transporter inhibition)	No dosage adjustment of Lamivudine and Zidovudine Tablets 150 mg/ 300 mg necessary, unless patient has renal impairment (section 4.2). When concomitant administration with trimethoprim + sulfamethaxazole is warranted, patients should be monitored clinically. High doses of trimethoprim + sulfamethoxazole for treating *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia and toxoplasmosis have not been studied and should be avoided.
Antifungal		
Fluconazole/Zidovudine (400 mg once daily/200 mg three times daily)	Zidovudine AUC ↑74% (UGT inhibition)	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8).
Antimalarial		
Atovaquone/Zidovudine (750 mg twice daily with food/200 mg three times daily)	Zidovudine AUC ↑33% Atovaquone AUC ↔	The clinical significance is not known.
Anticonvulsants		
Phenobarbital/Zidovudine	Interaction not studied. Potential to slightly decrease zidovudine plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
Phenytoin/Zidovudine	Phenytoin AUC ↑↓	Monitor phenytoin concentration.
Valproic acid/Zidovudine (250 mg or 500 mg three times daily/100 mg three times daily)	Zidovudine AUC ↑80% (UGT inhibition)	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8).
Opioids		
Methadone/Zidovudine (30–90 mg once daily/200 mg every 4 hours)	Zidovudine AUC ↑43% Methadone AUC ↔	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8). Methadone dosage adjustment may be required only occasionally.
Uricosuric		
Probenecid/ Zidovudine(500 mg four times daily/2 mg/kg three times daily)	Zidovudine AUC ↑106% (UGT inhibition)	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8).
Abbreviations	↑ = Increase ↔ = no significant change	↓ = decrease AUC = area under the concentration versus time curve

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV. Therefore, concomitant use of ribavirin with Lamivudine and Zidovudine Tablets 150 mg/ 300 mg is not recommended (see section 4.4), particularly in patients with a history of zidovudine-induced anaemia.
Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, dapsone, pyrimethamine, trimethoprim + sulfamethoxazole,
amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) and zidovudine
may increase the risk of adverse reactions. If concomitant therapy with Lamivudine and Zidovudine Tablets 150 mg/ 300 mg and any of these medicines is necessary then extra care should be taken to monitor renal function and haematological parameters and, if required, the dose of one or more agents should be reduced.

4.6 Pregnancy and breastfeeding

Pregnancy

No increased risk of birth defects have been reported for lamivudine or for zidovudine (www.apregistry.com). However, risks to the fetus cannot be ruled out.
The use in pregnant women of zidovudine alone, with subsequent treatment of the newborn infants, has been shown to

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PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, health care provider or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, health care provider or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. WHAT LAMIVUDINE AND ZIDOVUDINE TABLETS 150 MG/ 300 MG IS AND WHAT IT IS USED FOR

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg contains two active substances used to treat human immunodeficiency virus (HIV) infection: lamivudine and zidovudine. Both belong to a group of antiviral medicines, also known as antiretrovirals, called nucleoside analogue reverse transcriptase inhibitors (NRTIs).

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg is used with other antiretroviral medicines to treat HIV infection in adults, adolescents and children. Lamivudine and Zidovudine Tablets 150 mg/ 300 mg reduces the amount of HIV in your body, and keeps it at a low level. It also increases CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important for a healthy immune system and for helping your body to fight infection.

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg may improve your condition, but it is not a cure for HIV infection. HIV infection is spread by contact with blood of an infected person, and also by sexual contact. Therefore, even when you are taking antiretroviral medicines, you must continue to take appropriate precautions to avoid passing the HIV infection to other people.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE LAMIVUDINE AND ZIDOVUDINE TABLETS 150 MG/ 300 MG Do not take Lamivudine and Zidovudine Tablets 150 mg/ 300 mg:

- if you are allergic (hypersensitive) to lamivudine, zidovudine or to any of the other ingredients of Lamivudine and Zidovudine Tablets 150 mg/ 300 mg (listed in section 6, below).
- if you have a very low red blood cell count (severe anaemia) or a very low white blood cell count (neutropenia or leucopenia).

Warnings and precautions

It is important that your doctor or health care provider knows about all your symptoms even if you think they are not related to HIV infection. Your doctor or health care provider may decide to prescribe lamivudine or zidovudine as separate medicines instead of Lamivudine and Zidovudine Tablets 150 mg/ 300 mg.

- Discuss the use of Lamivudine and Zidovudine Tablets 150 mg/ 300 mg with your doctor or health care provider if you have kidney disease to ensure the doses of the active substances in Lamivudine and Zidovudine Tablets 150 mg/ 300 mg are suitable for you.
- Since low red blood cell count (anaemia) as well as low white blood cell count (neutropenia or leucopenia) may occur due to treatment with Lamivudine and Zidovudine Tablets 150 mg/ 300 mg, regular blood tests will be arranged to check for any problem.
- Please speak with your doctor or health care provider if you have had liver disease. Patients with chronic hepatitis B or C who are treated with antiretroviral medicines may require blood tests to check for liver function because they can develop very serious liver problems.
  If you have chronic hepatitis B, you should not stop your treatment without checking with your doctor or health care provider, otherwise you may have a recurrence of your hepatitis. This recurrence may be more severe if you have serious liver disease.
- Patients (especially woman) who are very overweight, and patients with liver disease, may be at higher risk of developing a rare, but serious side effect, called lactic acidosis (build up of lactic acid in the body). Lactic acidosis usually develops after a few months of treatment. Symptoms and signs that might indicate the development of lactic acidosis include deep rapid breathing, drowsiness and non-specific symptoms such as nausea, vomiting and stomach pain.
  While you are being treated with Lamivudine and Zidovudine Tablets 150 mg/ 300 mg, your doctor or health care provider will monitor you for any signs of lactic acidosis.

Other medicines and Lamivudine and Zidovudine Tablets 150 mg/ 300 mg

Tell your doctor, health care provider or pharmacist if you are taking, or have recently taken, any other medicines, and also if you begin taking any new medicine while you are taking Lamivudine and Zidovudine Tablets 150 mg/ 300 mg. This includes medicines obtained without a prescription and herbal medicines.

Tell your doctor about the following medicines, which may affect the action of Lamivudine and Zidovudine Tablets 150 mg/ 300 mg, or conversely, Lamivudine and Zidovudine Tablets 150 mg/ 300 mg may affect their action.

Medicines that should not be used with Lamivudine and Zidovudine Tablets 150 mg/ 300 mg

- Stavudine or emtricitabine to treat HIV infection.
- ribavirin or injections of ganciclovir to treat viral infections.
- high doses of trimethoprim + sulfamethoxazole, an antibiotic.

Some medicines interact with Lamivudine and Zidovudine Tablets 150 mg/ 300 mg

- valproic acid and phenytoin, to treat epilepsy
- interferon, to treat viral infections
- clarithromycin, an antibiotic—take clarithromycin at least 2 hours before taking Lamivudine and Zidovudine Tablets 150 mg/ 300 mg
- pyrimethamine, to treat malaria and other parasitic infections
- dapsone (unless used for prophylaxis), to prevent pneumonia and treat skin infections
- amphotericin, fluconazole or flucytosine, to treat fungal infections such as Candida
- pentamidine, atovaquone to treat parasitic infections
- probenecid, to treat gout and given with some antibiotics to make them more effective
- methadone, used as a 'heroin substitute'
- vincristine, vinblastine or doxorubicin, to treat cancer.

Pregnancy and breastfeeding

Pregnancy:

If you are pregnant, if you become pregnant or if you are planning to become pregnant talk to your doctor about the benefits and risks to you and your baby if you take Lamivudine and Zidovudine Tablets 150 mg/ 300 mg. If you become pregnant while you are taking Lamivudine and Zidovudine Tablets 150 mg/ 300 mg, your baby may be given extra check-ups (including blood tests). Children whose mothers took NRTIs (medicines like Lamivudine and Zidovudine Tablets 150 mg/ 300 mg) during pregnancy had a reduced risk of being infected with HIV. This benefit is greater than the risk of having side effects.

Be sure to tell your doctor immediately if you are or may be pregnant.

Breastfeeding:

If you are interested in breastfeeding your baby, you should discuss the risks and benefits with your doctor or healthcare provider.

Driving and using machines

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg may cause side effects such as dizziness, fatigue or headache, which can affect your ability to drive and to use machines. Therefore, don't drive or operate machines unless you are feeling well.

3. HOW TO TAKE LAMIVUDINE AND ZIDOVUDINE TABLETS 150 MG/ 300 MG

Always take Lamivudine and Zidovudine Tablets 150 mg/ 300 mg exactly as your doctor or health care provider has told you. Check with your doctor, health care provider or pharmacist if you're not sure.

Taking Lamivudine and Zidovudine Tablets 150 mg/ 300 mg

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg may be taken with food or between meals, swallowed with some water or another drink. If you cannot swallow the tablets, you may crush and take them immediately with a small amount of semi- solid food or drink. You must make sure that you take the whole dose.

Patients who weigh 25 kg or more: The usual daily dose of Lamivudine and Zidovudine Tablets 150 mg/ 300 mg is 1 tablet twice a day.

Patients who weigh less than 25 kg should be given another formulation containing lower amounts of lamivudine and zidovudine. Lamivudine and Zidovudine Tablets 150 mg/ 300 mg is not suitable for them.

If you take more Lamivudine and Zidovudine Tablets 150 mg/ 300 mg than you should

If you have taken too many tablets or if someone accidentally swallows some, there is no immediate danger. However, you should contact your doctor, health care provider or the nearest hospital emergency department for further advice.

If you forget to take Lamivudine and Zidovudine Tablets 150 mg/ 300 mg

If you accidentally miss a dose, take it as soon as you remember, and then continue as before. If your next dose is due in less than 6 hours, do not take the forgotten dose, but take the next regular dose when it is due. Do not take a double dose to make up for missed doses.

If you stop taking Lamivudine and Zidovudine Tablets 150 mg/ 300 mg

Because your medicine controls and does not cure your condition, you need to take it continuously. You should not stop treatment unless your doctor or health care provider tells you to.

If you have any further questions on the use of this product, ask your doctor, health care provider or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Lamivudine and Zidovudine Tablets 150 mg/ 300 mg can cause side effects, but not everybody gets them.

It is not always possible to differentiate unwanted effects of Lamivudine and Zidovudine Tablets 150 mg/ 300 mg from those caused by other medicines you are taking at the same time, and from the effects of the HIV disease itself.
It is important that you tell your doctor or health care provider of any change in your health.
Temporary, short-term side effects of antiretroviral medicines are common.
After you start taking Lamivudine and Zidovudine Tablets 150 mg/ 300 mg, some side effects, such as headache, nausea and vomiting, abdominal pain, diarrhoea and fatigue may occur. These are usually mild and disappear within a few weeks
during your treatment.

If you get side effects

Tell your doctor, health care provider or pharmacist if any side effect gets worse or is troublesome, or if you notice any side effects not listed in this leaflet.

Very common side effects

These affect ***more than 1 in 10*** people:

- headache
- feeling sick (nausea)

Common side effects

These affect ***1 in 100 to 1 in 10*** people:

- being sick (vomiting)
- diarrhoea
- stomach pains
- loss of appetite
- feeling dizzy
- tiredness, lack of energy

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg
21085792

Lamivudine and Zidovudine Tablets 150 mg/ 300 mg
21085792

PACKAGING DEVELOPMENT

Product Name : Lamivudine and Zidovudine Tablets 150 mg/ 300 mg	**Material No.:** 21085792	**Version :** 01	**Item :** Leaflet	**Co-ordinator :** Sachita	**Artist :** Ramashankar	**Date:** 04-09-2020
Colours : **BLUE WOOL TEST VALUE 5-8 (LIGHT FASTENING DATA)** ■ Black				**INK:** Oil based Ink from DIC OR MICRO		
Design : Folded (Booklet)	**Reference :** 21060141			**Software :** Indesign CC		
Fonts : --------	**Links :** NA					
Actual Size : 500 x 350 mm	**Size after Folding :** 125 x 175 mm	**Pharmacode:** 4579_MINI	**Grain Direction :** Parallel to length			**Screen : # ---**
Material: 40 GSM ITC Paper [Set of 40 Leaflets tightly packed with Poly Laminated paper (width: 70 mm)			**Varnish : -----**	**Artwork Print Size :** ☐ actual ☐ scaled		
Path : RAMA - F:\JOBS\OTC\QCIL Uganda\ 21085792 Lamivudine and Zidovudine Tablets 150-300 mg Leaflet (Common) QCIL Uganda.indd						

- **Instructions / Remark :**
- Any deviation must be brought to the notice of packaging development co-ordinator immediately.
- For any clarification, please contact packaging development co-ordinator immediately.
  NO CHANGES IN ARTWORK SHOULD BE DONE BY THE PRINTER
- The printer should verify the e-proof against the approved artwork before submitting for approval and the e-proof should have printer details .

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Artwork	☐	☐		
Spell check	☐	☐		

PROOFLESS

- fever (high temperature)
- general feeling of being unwell
- difficulty in sleeping (insomnia)
- muscle pain and discomfort
- joint pain
- cough
- irritated or runny nose
- skin rash
- hair loss (alopecia).

Common side effects that might show up in blood tests are:
- a low red blood cell count (anaemia) or low white blood cell count (neutropenia or leucopenia)
- an increase in the level of liver enzymes
- an increased amount of bilirubin (a substance produced in the liver).

Uncommon side effects
These may affect ***1 in 1000 to 1 in 100*** people:
- feeling breathless
- wind (flatulence)
- itching
- muscle weakness.

An uncommon side effect that may show up in blood test is:
- decrease in the number of cell fragments involved in blood clotting (thrombocytopenia) or in all kinds of blood cells (pancytopenia).

Rare side effects
These may affect ***1 in 10 000 to 1 in 1000*** people:
- serious allergic reaction causing swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing
- liver disorders, such as jaundice, enlarged liver or fatty liver, inflammation (hepatitis)
- lactic acidosis (see below, 'Other possible side effects of combination therapy for HIV')
- inflammation of the pancreas (pancreatitis)
- chest pain; damage to the heart muscle (cardiomyopathy)
- fits (convulsions)
- feeling depressed or anxious, not being able to concentrate, feeling drowsy
- indigestion, taste disturbance
- changes in the colour of your nails, skin or the skin inside your mouth
- a flu-like feeling – chills and sweating
- tingling in the skin ('pins and needles')
- arms and legs feeling weak
- muscle damage
- numbness
- needing to pass urine more often
- enlarged breasts in men.

Rare side effects that may show up in blood tests are:
- an increase in an enzyme called amylase
- inability to produce new red blood cells (pure red cell aplasia).

Very rare side effects
These may affect ***fewer than 1 in 10 000*** people:
- blood tests showing an inability to produce new red and white blood cells (aplastic anaemia).

Other possible side effects of combination therapy for HIV infection
Combination therapy, including Lamivudine and Zidovudine Tablets 150 mg/ 300 mg, may cause other conditions to develop during HIV treatment.

Old infections may flare up. People with advanced HIV infection (AIDS) have a weakened immune system, and can harbour germs. When these people start treatment, they may find that infections they had caught in the past, flare up. This is probably caused by the body's immune system recovering and starting to fight these infections.
If you get any symptoms of infection while you're taking Lamivudine and Zidovudine Tablets 150 mg/ 300 mg: Tell your doctor immediately. Don't take other medicines for the infection without your doctor's advice.

Your body shape may change. People taking antiretroviral medicines for HIV may find that their body shape changes, because of changes in fat distribution:
- Fat may be lost from the legs, arms or face
- Extra fat may build up around the tummy (abdomen), or on the breasts or internal organs
- Fatty lumps ('buffalo hump') may appear on the back of the neck.

It is not yet known what causes these changes, or if they have any long-term effects on your health. Tell your doctor if you notice changes in your body shape.

Lactic acidosis, a rare but serious side effect. Some people taking Lamivudine and Zidovudine Tablets 150 mg/ 300 mg, or other medicines like it (NRTIs), develop a rare condition called lactic acidosis, together with an enlarged liver.
Lactic acidosis is caused by a build up of lactic acid in the body and usually develops after a few months of treatment. It can be life-threatening, causing failure of internal organs. Lactic acidosis is more likely to develop in people who have liver disease, or in very overweight people, especially women. Signs of lactic acidosis include:
- deep, rapid, difficult breathing
- drowsiness
- numbness or weakness in the limbs
- feeling sick (nausea), being sick (vomiting)
- stomach pain.

During your treatment, your doctor will monitor you for signs of lactic acidosis. If you have any of the symptoms listed above, or any other symptoms that worry you:
See your doctor as soon as possible.

You may have problems with your bones. Some people taking combination therapy, including Lamivudine and Zidovudine Tablets 150 mg/ 300 mg, may develop a condition called osteonecrosis. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:
- if they have been taking combination therapy, including Lamivudine and Zidovudine Tablets 150 mg/ 300 mg, for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune system is very weak
- if they are overweight.

Signs of osteonecrosis include:
- stiffness in the joints
- aches and pains (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms, tell your doctor or health care provider.

Other effects may show up in blood tests. Lamivudine and Zidovudine Tablets 150 mg/ 300 mg can also:
- increase levels of sugar and fats (triglycerides and cholesterol) in the blood
- reduce the effect of insulin (so if you have diabetes, you may have to change your insulin dose to control your blood sugar).

5. HOW TO STORE LAMIVUDINE AND ZIDOVUDINE TABLETS 150 MG/ 300 MG
Keep this medicine out of the sight and reach of children. Do not store above 30°C.
Do not use Lamivudine and Zidovudine Tablets 150 mg/ 300 mg after the expiry date, which is stated on the container label. The expiry date refers to the last day of that month.

Do not use Lamivudine and Zidovudine Tablets 150 mg/ 300 mg if the tablet looks different from the description below, under 'Further Information'.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. This will help to protect the environment.

6. FURTHER INFORMATION What Lamivudine and Zidovudine Tablets 150 mg/ 300 mg contains
The active ingredients are 150 mg lamivudine and 300 mg zidovudine.
The other ingredients are colloidal silicon dioxide, microcrystalline cellulose, sodium starch glycollate, magnesium stearate, hydroxypropyl methyl cellulose, talc, titanium dioxide and propylene glycol

What Lamivudine and Zidovudine Tablets 150 mg/ 300 mg looks like and contents of the pack
Lamivudine and Zidovudine Tablets 150 mg/ 300 mg tablets are white colored, film coated, oblong, biconvex tablets with 'DVR' embossed on one side and plain on the other.
Lamivudine and Zidovudine Tablets 150 mg/ 300 mg film-coated tablets are provided in HDPE bottles (65 cc or 85 cc, containing 1 gm silica desiccant) containing 60 tablets and blister of 10 or 14 tablets.

For any information about this medicinal product, please contact the supplier and manufacturer
Mfd. by
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Luzira Industrial Park,
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E-mail : info@ciplaqcil.co.ug
Website : www.ciplaqcil.co.ug

For any information about this medicinal product, please contact the supplier.

This leaflet was last approved in February 2013.

Detailed information on this medicine is available on the World Health Organization (WHO) web site:
http://www.who.int/prequal/

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reduce the rate of maternal-fetal transmission of HIV-infection. However, no such data are available for lamivudine.

Breastfeeding
Both lamivudine and zidovudine are present in breast milk at concentrations similar to those in the serum. The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted before advising mothers on breastfeeding.

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

4.8 Undesirable effects
As Lamivudine and Zidovudine Tablets 150 mg/ 300 mg contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of added toxicity with concurrent administration of the two compounds.

The most frequently reported adverse reactions are headache and nausea. The most common serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia (see section 4.4).
Adverse events considered to be at least possibly related to treatment with zidovudine and lamivudine, 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 of lamivudine, zidovudine, and lamivudine/zidovudine as a fixed-dose combination are listed. Since they are reported voluntarily from a population of unknown size, the frequency cannot be estimated (frequency category: 'unknown'). These events have been included on the basis of their seriousness, number of reports, or potential causal connection to lamivudine, zidovudine, and lamivudine/zidovudine as fixed-dose combination.

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, anorexia
Unknown: changes in distribution of body fat, hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, hyperlactataemia (see section 4.4)

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
Common: Cough, nasal symptoms
Uncommon: Dyspnoea

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting, abdominal pain or cramps, diarrhoea
Uncommon: Flatulence
Rare: Pancreatitis, raised serum amylase, oral mucosa pigmentation, taste perversion, dyspepsia

Hepatobiliary disorders
Common: Elevated liver enzymes and bilirubin
Rare: Hepatitis, severe hepatomegaly with steatosis

Skin and subcutaneous tissue disorders
Common: Rash, hair loss
Uncommon: Pruritus
Rare: Nail and skin pigmentation, urticaria, sweating, angioedema

Musculoskeletal and connective tissue disorders
Common: Arthralgia, myalgia
Uncommon: Myopathy *Rare*: Rhabdomyolysis *Unknown*: osteonecrosis

Renal and urinary disorders
Rare: Urinary frequency

Reproductive system and breast disorders
Rare: Gynaecomastia

General disorders and administration site disorders:
Common: Malaise, fatigue, fever
Uncommon: Asthenia, generalised pain
Rare: Chest pain, influenza-like syndrome, chills
Unknown: Immune reconstitution syndrome (see section 4.4) See also sections 4.4 and 4.5

4.9 Overdose
There is limited experience of overdosage with lamivudine/zidovudine. No specific signs and symptoms have been identified following acute overdose with zidovudine or lamivudine apart from those listed as undesirable effects. No fatalities occurred and the patients recovered. If overdose occurs patients should be monitored for toxicity (see section 4.8), and standard supportive treatment given as necessary. Since elimination of lamivudine and the glucuronide metabolite of zidovudine are enhanced by haemodialysis, continuous haemodialysis could be used in the treatment of overdosage (but this has not been studied).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC Code J05AR01

Mechanism of action:
Lamivudine and zidovudine are nucleoside analogues that are active against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both compounds are metabolised intracellularly to their active moieties, lamivudine 5'-triphosphate (TP) and zidovudine 5'-triphosphate 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 is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

Clinical efficacy:
In clinical trials, lamivudine in combination with zidovudine reduces HIV-1 viral load and increases CD4 cell count. Clinical end-point data indicate that lamivudine in combination with zidovudine, results in a significant reduction in the risk of disease progression and mortality. In a trial of zidovudine and lamivudine in combination with efavirenz, 68% of subjects achieved plasma HIV RNA < 50 copies/ml after 48 weeks, by intention-to-treat analysis. Lamivudine and zidovudine have been widely used as components of antiretroviral combination therapy with other antiretroviral agents of the same class (NRTIs) or different classes (protease inhibitors, non-nucleoside reverse transcriptase inhibitors).

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). *In vitro* data suggest that continuation of lamivudine in antiretroviral regimen despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, available clinical data are very limited and preclude any reliable conclusion in the field. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should be considered only 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 class of NRTI, upon virological failure with combination therapy including zidovudine and lamivudine, underscores the importance of early detection of virological failure. Delayed detection of virological failure may severely limit the options for second-line therapy.

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

5.2 Pharmacokinetic properties

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

Following single dose of Lamivudine and Zidovudine Tablets 150 mg/ 300 mg in healthy volunteers, mean of lamivudine and zidovudine Cmax values were 1.7968 μg/ml and 2.0618 μg/ml, respectively and the corresponding values for AUC∞ were 7.8499 μg hour/ml and 2.4596 μg hour/ml, respectively. The median lamivudine and zidovudine tmax values were 1.10 hours and 0.50 hours respectively.

The extent of lamivudine and zidovudine absorption (AUCT) and estimates of half-life following administration of a respective fixed combination product (Combivir, GSK) with food were similar when compared to fasting subjects, although the rates of absorption (Cmax, tmax) were slowed. Based on these data Lamivudine and Zidovudine Tablets 150 mg/ 300 mg may be administered with food or between meals.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to affect the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data assuming that the patient ingests the full dose immediately after crushing the tablets.

Distribution
Intravenous studies with lamivudine and zidovudine showed that the mean apparent volume of distribution is 1.3 litre/kg and 1.6 litre/kg respectively.

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

Zidovudine plasma protein binding is 34–38%. Drug interactions involving binding site displacement are not anticipated with Lamivudine and Zidovudine Tablets 150 mg/ 300 mg.

Metabolism
Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominantly cleared unchanged by renal excretion. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5–10%) and low plasma protein binding.
The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50–80% of the administered dose eliminated by renal excretion. 3'-amino-3'- deoxythymidine has been identified as a metabolite of zidovudine following intravenous dosing.

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 litre/hour/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. Dose reduction is recommended for patients with creatinine clearance ≤ 50 ml/minute (see section 4.2).

In studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6 litre/hour/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 litre/hour/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

Special populations:

Pregnancy: The pharmacokinetics of lamivudine and zidovudine during pregnancy were similar to that of non-pregnant women.

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

In children over the age of 5–6 months, the pharmacokinetic profile of zidovudine is similar to that in adults. Zidovudine is well absorbed from the gut and at all dose levels studied in adults and children, the bioavailability was between 60–74%.

5.3 Preclinical safety data
Neither lamivudine nor zidovudine is mutagenic in bacterial tests, but like many nucleoside analogues they show activity in mammalian *in vitro* tests such as the mouse lymphoma assay. Lamivudine has not shown any genotoxic activity in *in vivo* studies at doses that produced 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 in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at exposures equivalent to those in humans. That study demonstrated that fetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple fetal 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. No other zidovudine-related tumours were observed in either sex of either species.

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

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months, with exposure beginning prenatally on gestation day 10. Treatment-related findings were limited to late-occurring vaginal epithelial tumours, which were seen with a similar incidence and time of onset as in the standard oral carcinogenicity study. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
CORE
Colloidal silicon dioxide
Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate
COATING
Hydroxypropyl methyl cellulose
Talc
Titanium dioxide
Propylene glycol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 30°C

6.5 Nature and contents of container
PVC/PVDC/Al blister of 10 or 14 tablets

HDPE bottle pack (cylindrical, white, opaque, induction-sealed 85 cc HDPE bottles fitted with white 38mm HDPE continuous thread closures and containing 1gm silica gel desiccant) of 60 tablets.

HDPE bottle pack (cylindrical, white, opaque, induction-sealed 65 cc HDPE bottles fitted with white 45mm HDPE continuous thread closures and containing 1gm silica gel desiccant) of 60 tablets

6.6 Instructions for use and handling and disposal
No special requirements.

7. Supplier and Manufacturer
Mfd. by
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