

**SUMMARY OF PRODUCT CHARACTERISTICS**

**1. NAME OF THE MEDICINAL PRODUCT**

Lamivudine 150 mg and Zidovudine 300 mg Tablets

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains Lamivudine 150 mg and Zidovudine 300 mg.  
For excipients see 6.1

**3. PHARMACEUTICAL FORM**

Film-coated tablet

White film coated tablet embossed with "ZLM" on one side.

**4. CLINICAL PARTICULARS****4.1 Therapeutic indications**

The fixed combination of lamivudine and zidovudine is indicated in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents over 12 years of age.

**4.2 Posology and method of administration**

Oral use.

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

The recommended dose of Zidolam Tablets in adults and adolescents over 12 years of age is:

- One tablet twice daily.

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

Zidolam Tablets may be taken with or without food (*1*).

Children:

Zidolam Tablets is not indicated for children < 12 years of age, as appropriate dose reduction for the weight of the child cannot be made.

Elderly:

Special care is advised in this age group due to associated changes such as decrease in renal function and alteration of haematological parameters.

**Dose adjustment**

Renal Impairment:

Since dose adjustment may be necessary in patients with renal impairment (creatinine clearance  $\leq$  50 ml/min), it is recommended that separate preparations of lamivudine and zidovudine be administered (see section 4.4) (2, 3).

**Hepatic impairment:**

No dose adjustments are 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 reductions of zidovudine should be considered in patients whose haemoglobin concentrations or neutrophil counts fall to clinically significant levels, it is recommended that separate preparations of lamivudine and (if appropriate) zidovudine be administered (see section 4.4).

**4.3 Contraindications**

Zidolam Tablets is contraindicated in patients with

- Hypersensitivity to lamivudine, zidovudine or to any of the excipients contained in the formulation,
- With abnormally low neutrophil counts ( $< 0.75 \times 10^9/l$ ) (see section 4.4),
- With abnormally low haemoglobin levels ( $< 7.5 \text{ g/dl}$  or  $4.65 \text{ mmol/l}$ ) (see section 4.4)

**4.4 Special warnings and special precautions for use**

Lamivudine/zidovudine should only be used in combination with abacavir in the treatment of antiretroviral therapy (ART) naïve patients when a regimen based on a protease inhibitor (PI) or a non-nucleoside inhibitor of reverse transcriptase (NNRTI) cannot be used (4).

**Dose adjustments:**

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 these medicinal products.

**Opportunistic infections:**

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

**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 low serum vitamin B12 levels, and usually after at least 4-6 weeks of therapy.

Therefore, it is recommended to monitor haematological parameters in patients receiving Zidolam Tablets, e.g. as follows:

- In advanced HIV disease: at least every two weeks during the first three 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 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, 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 Zidolam Tablets 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 NRTI use. It may occur after a few to several months of treatment. Patients with hyperlactatemia 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 (5). Patients at increased risk should be closely monitored clinically. Screening for hyperlactatemia in asymptomatic patients treated with NRTIs, however, is not recommended (6). Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs, including zidovudine/lamivudine. Lactic acid levels > 10 mmol/l usually are 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 *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia and neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). 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 current national 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 e.g. with older age of the patient, 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 pre-existing severe immune deficiency, typically in 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.

#### Liver disease:

Caution should be exercised when administering Zidolam 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 Zidolam 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 that are treated with combination antiretroviral therapy, have an increased risk of severe and potentially fatal hepatic adverse events.

Patients with pre-existing liver dysfunction have an increased frequency of liver function abnormalities during combination 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.

#### Osteonecrosis:

Although the etiology 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 and/or long-term exposure to combination ART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

#### 4.5 Interaction with other medicinal products and other forms of interaction

As Zidolam Tablets contains lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur with Zidolam Tablets. Whereas lamivudine undergoes limited metabolism and is almost completely eliminated via the kidneys, zidovudine is primarily eliminated by hepatic conjugation, to form an inactive glucuronidated metabolite. The following list of interactions listed should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised.

Interactions relevant to lamivudine:

Because of overlapping resistance and lack of additive antiretroviral effects, lamivudine should not be co-administered with emtricitabine.

Co-administration with trimethoprim / sulfamethoxazole results in a 40% increase in lamivudine exposure (13) because of the trimethoprim component. Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

Lamivudine does not inhibit the cytochrome P450 isoform CYP3A.

Interactions relevant to zidovudine:

Since zidovudine and stavudine act antagonistic in vitro, Zidolam Tablets should not be used concomitantly with stavudine.

Co-administration of zidovudine with ribavirin leads to additive or synergistic bone marrow toxicity. For this reason, zidovudine should be replaced by an alternative antiretroviral agent in patients treated with ribavirin(8).

Co-administration of zidovudine with rifampicin decreases the exposure to zidovudine. However, the clinical significance of this is unknown. Dose modifications of zidovudine in this situation have not been formally evaluated.

Probenecid, valproic acid and fluconazole increase the exposure to zidovudine. Patients should be closely monitored for haematological toxicity.

Clarithromycin tablets reduce the absorption of zidovudine. The clinical relevance is unclear. However, this effect can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.

Atovaquone and methadone have been shown to increase exposure to zidovudine. The clinical relevance is unknown.

Phenytoin plasma levels have been reported to be altered in either way in patients receiving zidovudine. Thus, phenytoin levels should be carefully monitored in patients receiving Zidolam Tablets and phenytoin.

Concomitant treatment with therapeutic doses of dapsone (which may cause haemolytic anaemia) or of potentially nephrotoxic or myelosuppressive agents (e.g. systemic pentamidine, pyrimethamine, cotrimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine. If concomitant therapy with any of these drugs is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dose of the concomitantly administered drug should be reduced. If modification of the zidovudine dosage is necessary, separate preparations of lamivudine and zidovudine should be administered (see sections 4.2 and 4.4).

Clinical data do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole, aerosolized pentamidine, pyrimethamine, dapsone and aciclovir at the doses used in prophylaxis of opportunistic infections.

Zidovudine does not inhibit the cytochrome P450 isoform CYP3A.

#### 4.6 Pregnancy and lactation

*Pregnancy:* No increased risk of birth defects has been reported for lamivudine or zidovudine ([www.apregistry.com](http://www.apregistry.com)). However, risks to the fetus cannot be ruled out.

*Nursing Mothers:* Both lamivudine and zidovudine are excreted into the breast milk of lactating mothers (9). Because of the potential for HIV transmission and adverse effects caused by lamivudine and zidovudine in nursing infants, HIV-infected mothers should be instructed not to breastfeed.

#### 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 Zidolam Tablets should be borne in mind when considering the patient's ability to drive or operate machinery.

#### 4.8 Undesirable effects

As Zidolam Tablets 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 following the concurrent administration of the two agents.

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 ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1000$ ) or very rare ( $\leq 1/10,000$ ). In addition, adverse events identified during post-approval use of lamivudine, zidovudine, and/or lamivudine/zidovudine as a fixed-dose combination are listed (frequency category: 'unknown'). Since they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, number of reports, or potential causal connection to lamivudine, zidovudine, and/or lamivudine / zidovudine as fixed-dose combination.

##### Blood and lymphatic systems disorders

*Common:* Anaemia, neutropenia (10, 11), leucopenia (12-15),

*Uncommon:* Thrombocytopenia, pancytopenia

*Rare:* Pure red cell aplasia

*Very rare:* Aplastic anaemia.

##### Metabolic and nutrition disorders

*Rare:* Lactic acidosis (16, 18-24)

*Unknown:* changes in distribution of body fat (12), hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, hyperlactataemia (see section 4.4)

##### Psychiatric disorders

*Rare:* anxiety, depression (17).

##### Nervous system disorders

*Very common:* Headache (12)

*Common:* Dizziness, insomnia (10, 25-27)

*Rare:* Paraesthesia, somnolence, loss of mental acuity, convulsions (17)

##### Cardiac disorders

*Rare:* Cardiomyopathy (17).

##### Respiratory, thoracic and mediastinal disorders

*Uncommon:* Dyspnoea (17).

*Rare:* cough (17).

#### Gastrointestinal disorders

*Very common:* Nausea (12-14)

*Common:* Vomiting, abdominal pain and diarrhoea (10, 13, 14, 28)

*Uncommon:* Flatulence (17)

*Rare:* Pancreatitis, oral mucosa pigmentation, taste perversion, dyspepsia (17)

#### Hepatobiliary disorders

*Common:* Elevated liver enzymes and bilirubin (17)

*Rare:* Hepatitis (29), severe hepatomegaly with steatosis (17)

#### Skin and subcutaneous tissue disorders

*Common:* Rash (29), hair loss (30)

*Uncommon:* Pruritus (17)

*Rare:* Nail and skin pigmentation, urticaria, sweating (17).

#### Musculoskeletal and connective tissue disorders

*Common:* Myalgia (17)

*Uncommon:* Myopathy (17), osteonecrosis

#### Renal and urinary disorders

*Rare:* Urinary frequency (17)

#### Reproductive system and breast disorders

*Rare:* Gynaecomastia (17)

#### General disorders and administration site disorders:

*Common:* Malaise (17), fatigue (13).

*Uncommon:* Asthenia, fever, generalized pain (17)

*Rare:* Chest pain, influenza-like syndrome, chills (17)

*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 applied 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 (although this has not been studied).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside analogue, ATC Code J05A F30

Lamivudine and zidovudine are nucleoside analogues that have activity against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both medicinal products 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 has been shown to reduce HIV-1 viral load and increase CD4 cell count (15, 31-44). 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 recently published 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 (15). 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 (PIs, NNRTIs).

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. For this reason continued lamivudine treatment, despite high-grade resistance, may sometimes be of value, in order to prevent reversion to wild type at this amino acid position. This particularly pertains to treatment regimens following multiple virological failures, where viral response to the new drug combination may be compromised from the outset. The benefit of lamivudine in this situation, however, is substantially lower than when treating wild-type virus (45).

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 analog 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 (46).

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 (47).

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 Zidolam Tablets administration in healthy volunteers, mean (CV) lamivudine and zidovudine  $C_{max}$  values were  $1.2862 \pm 0.4258$  µg/ml (33.10 %) and  $2.0237 \pm 0.8891$  µg/ml (43.93 %), respectively and the corresponding values for  $AUC_{0-t}$  were  $5.9480 \pm 1.4775$  µg.hr/ml (24.84 %) and  $2.6860 \pm 0.7785$  µg.hr/ml (28.98 %) respectively. The mean (range) lamivudine and zidovudine  $t_{max}$  values were  $1.19 \pm 0.70$  hours and  $0.58 \pm 0.44$  hours respectively.

The extent of lamivudine and zidovudine absorption ( $AUC_T$ ) 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 ( $C_{max}$ ,  $t_{max}$ ) were slowed. Based on these data Zidolam Tablets may be administered with or without food.

### Distribution

Intravenous studies with lamivudine and zidovudine showed that the mean apparent volume of distribution is 1.3 and 1.6 l/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% to 38%. Drug interactions involving binding site displacement are not anticipated with Zidolam 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. 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 approximately 22 hours (48). 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. Dose reduction is recommended for patients with creatinine clearance ≤ 50 ml/min (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 l/h/kg. The half-life of intracellular zidovudine triphosphate has been estimated to around 7 hours (48). 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.

#### *Pharmacokinetics in pregnancy*

The pharmacokinetics of lamivudine and zidovudine were similar to that of non-pregnant women.

### **5.3 Preclinical safety data**

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 demonstrated evidence of causing an increase in 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 foetal abnormalities was observed at lower doses.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose, colloidal anhydrous silica, sodium starch glycollate, magnesium stearate, opadry white Y-1-7000.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

HDPE Bottles: 3 years,  
Blister Packs: 2 years

### 6.4 Special precautions for storage

Store below 25°C in the original package in order to protect from moisture.

### 6.5 Nature and contents of container

60 film coated tablets packed in milk white HDPE containers sealed with aluminium foil and 10 film coated tablets packed in blister packs (10 blisters per carton).

### 6.6 Instructions for use and handling and disposal

No special requirements.

## 7. SUPPLIER

### M/s. Hetero Labs Limited

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## 8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

HA152

**9. DATE OF FIRST PREQUALIFICATION/RENEWAL OF PREQUALIFICATION**

May 2006

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

August 2007. Section 6 & 7 updated in May 2011.

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