ARTWORK FOR SUBMISSION: Malaysia

FPO

ARROW-LZ

Lamivudine 150mg &
Zidovudine 300mg Tablets USP

PRODUCT DESCRIPTION
White to off - white coloured, oval shaped film-coated tablets, with LZ debossed on one side and breakline on other side.

COMPOSITION
Each film coated tablet contains Lamivudine150 mg and Zidovudine300 mg.

PHARMACOLOGY
Lamivudine and zidovudine are potent, selective inhibitors of HIV-1 and HIV-2.

Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Both active substances are metabolized sequentially by intracellular kinases to 5' - triphosphate (TP). Lamivudine-TP and zidovudine-TP are substrates for and competitive inhibitors of HIV reverse transcriptase. However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine-TP and Zidovudine-TP show significantly less affinity for host cell DHA polymerases. In vitro, Lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines and to a variety of bone marrow progenitor cells. Lamivudine therefore has a high therapeutic index in vitro.

PHARMACODYNAMICS
Lamivudine in combination with Zidovudine has been shown to reduce HIV-1 viral load and to increase CD4 cell counts. Clinical endpoint data indicate that Lamivudine in combination with Zidovudine alone or in combination with Zidovudine – containing treatment regimens results in a significant reduction in the risk of disease progression and mortality.

Individually, Lamivudine and Zidovudine therapy has resulted in HIV clinical isolates, which show reduced sensitivity in vitro to the nucleoside analogue to which they have been exposed. Evidence from clinical studies show that Lamivudine Plus Zidovudine delays the emergence of Zidovudine- resistance isolates in individuals with no prior antiretroviral therapy.

Lamivudine and Zidovudine have been widely used as components of antiretroviral combination therapy with other antiretroviral agents of the same class (nucleoside reverse transcriptase inhibitors) or different classes (protease inhibitors, non-nucleoside reverse transcriptase inhibitors.)

Multiple drug antiretroviral therapy containing Lamivudine has been shown to be effective in antiretrovirally-naive patients as well as in patients presenting with viruses containing the Mt 84V mutations.

PHARMACOKINETICS

Absorption

Lamivudine and Zidovudine are well-absorbed from the gut. The bioavailability of oral Lamivudine in adults is normally between 80-85% and for Zidovudine 60-70%.

Distribution
IV studies with Lamivudine and Zidovudine showed that the mean apparent volume of distribution is

1.3 and 1.6 L/kg, respectively. Lamiv udine 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%. Interactions with medicinal products involving binding site displacement are not anticipated with Lamivudine 150 mg and Zidovudine 300 mg Tablet.

Data show that Lamivudine and Zidovudine penetrate the central nervous system and reach the cerebrospinal fluid (CSF). The mean ratios of CSF/serum Lamivudine and Zidovudine concentration 2- 4 hrs after oral administration were approximately 0.12 and 0.5 respectively. The true extent of penetration of Lamivudine or relationship with any clinical efficacy is unknown.

Metabolism
Metabolism of Lamivudine is a minor route of elimination. Lamivudine is predominately cleared by renal excretion of the unchanged active substance. The likelihood of metabolic interactions with Lamivudine is low due to the small extent of hepatic metabolism 95-10% and low plasma 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 (AMT) has been identified as a metabolite of Zidovudine following IV dosing.

Elimination
The observed Lamivudine half-life of elimination is 5-7 hrs. The mean systemic clearance of Lamivudine is approximately 0.32 L/hr /kg, with predominantly renal clearance (>70%) via the organic cationic transport system.

From studies with Zidovudine IV, the mean terminal half-life was 1.1 hrs and the mean systemic clearance was 1.6 L/hr/kg. Renal clearance of Zidovudine is estimated to be 0.34 L/hr/kg, indicating glomerular filtration and active tubular secretion by kidneys.

Special Populations

Impaired Renal Function

Lamivudine elimination is affected by renal dysfunction, due to decrease renal clearance. Dose reduction is required for patients with creatinine clearance of <50 ml/min. Zidovudine concentrations have also been shown to be increased in patients with advanced renal failure.

Impaired Hepatic Function
Accumulation of Zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Dosage adjustment of Zidovudine may be necessary in patients with severe hepatic impairment.

Elderly:
The pharmacokinetics of Lamivudine and Zidovudine have not been studied in patients >65 years.

Pregnancy:
The pharmacokinetics of Lamivudine and Zidovudine were similar to that of nonpregnant adults. In humans, consistent with passive transmission of Lamivudine across the placenta, Lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery. Zidovudine was measured in plasma and gave similar results to those observed for Lamivudine.

INDICATIONS
Lamivudine and Zidovudine 300 mg Tablets in combination with other antiretroviral agents are indicated for the treatment of HIV infection.

DOSAGE
Adult and Children (>12 years)

The recommended oral dose is 1 tablet of Lamviudine150 mg and Zidovudine 300mg Tablets twice daily.

Dose Adjustment
Because it is a fixed-dose combination, lamivudine and zidovudine should not be prescribed for patients requiring dosage adjustment such as those with reduced renal function, mild to moderate impaired hepatic function or liver cirrhosis.

Children (<12 years)

Lamivudine 150 mg and Zidovudine 300 mg Tablets is not indicated for children < 12 years.

Route of Administration
Oral

CONTRAINDICATIONS
Patients with known hypersensitivity to any of the components of the product; patients

With abnormally low neutrophil counts (<0.75 x 109/L), or abnormally low haemoglobin levels (<7.5 g/dL or 4.65 mmol/L).

WARNING AND PRECAUTIONS
It is recommended that separate preparations of Lamivudine and Zidovudine should be administered in cases where dosage adjustment is necessary. Patients should be cautioned about the concomitant use of self-administered medications. Patients should be advised that current antiretroviral therapy, including Lamivudine 150 mg and Zidovudine 300 mg Tablets has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Patients treated with Lamivudine 150 mg and Zidovudine300 mg Tablets or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physician experienced in the treatment of HIV infection.

Haematological
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- 1500 mg/day), in patients with advanced HIV disease and in those who had poor marrow reserve prior to treatment. Haematological parameters should therefore be carefully monitored in patients receiving Lamivudine 150 mg and Zidovudine 300 mg Tablets.

These haematological effects are not usually observed before 4-6 weeks therapy. For patients with advanced symptomatic HIV disease , it is generally recommended that blood tests are performed at least every 2 weeks for the first 3 months of therapy and at least monthly thereafter. In patients with early HIV disease, haematological adverse reactions are infrequent. Depending on the overall condition of the patient, blood tests may be performed less often, eg, every 1-3 months.

Additionally, dosage adjustment of Zidovudine may be required if severe anaemia or myelosuppresison occurs during treatment with Lamivudine 150 mg and Zidovudine 300 mg Tablets, or in patients with preexisting bone marrow compromise eg, haemoglobin <9 g/dl (5.59 mmol/L) or neutrophil count < 1 x 109/L. As dosage adjustment of Lamivudine150 mg and Zidovudine300 mg Tablets is not possible, separate preparations of Zidovudine and Lamivudine should be used.

Pancreatitis
Cases of pancreatitis have occurred rarely in patients treated with Lamivudine and Zidovudine. However, it is not clear whether these cases were due to treatment with the medicinal product or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of Lamivudine150 mg and Zidovudine 300 mg Tablets until diagnosis of pancreatitis is excluded.

Lactic Acidosis/Severe Hepatomegaly with Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including Lamivudine and Zidovudine. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalized weakness, anorexia and sudden unexplained weight loss, gastrointestinal and respiratory symptoms (dyspnoea and tachypnoea).

Caution should be exercised when administering Lamivudine 150 mg and Zidovudine300 mg Tablets to any patient and particularly to those with known risk factors for liver disease. Treatment with Lamivudine150 mg and Zidovudine 300 mg Tablets should be suspended in any patient who develops

clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Fat Redistribution
Redistribution/ accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump, , peripheral and facial wasting, breast enlargement, elevated serum lipid and blood glucose levels have been observed either separately or together in some patients receiving combination antiretroviral therapy.

While all members of the protease inhibitor (PI) and nucleoside reverse transcriptase inhibitor (NRTI) classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicated that there are differences in the risk between individual members of the respective therapeutic classes.

In addition, lipodystrophy syndrome has a multifactorial aetiology eg, with HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles. The long- term consequences of these events are currently unknown.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed a clinically appropriate.

Immune Reconstitution Syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions or aggravation of symptoms. Typically, such reactions have been observed within the 1st few weeks or months of initiation of antiretroviral therapy. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and Pneumocystis jiroveci (P carinri) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

Patients Co-Infected with Hepatitis B Virus
Some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of Lamivudine which may have more severe consequences in patients with decompensated liver disease. If Lamivudine 150 mg and Zidovudine 300 mg Tablets is discontinued in patients co-infected with HBV, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Effects on the Ability to Drive of Operate Machinery
There have been no studies to investigate the effect of lamivudine or Zidovudine

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Front Side

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on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substances. Nevertheless, the clinical status of the patient and the adverse event profile of Lamivudine and Zidovudine should be borne in mind when considering the patient's ability to drive or operate machinery.

DRUG INTERACTIONS

Interaction Relevant to Lamivudine

The likelihood of metabolic interactions with Lamivudine is low due to limited metabolism and plasma protein-binding, and almost complete renal elimination of unchanged Lamviudine.

Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system eg, Trimethoprim. Other active substance (eg, Ranitidine, Cimetidine) are eliminated only in part by this mechanism and were shown not to interact with Lamviudine.

Active substances shown to be predominantly excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with Lamivudine.

Trimethoprim:

Administration of Trimethoprim 160mg/sulfamethoxazole 800 mg (Co-trimoxazole) once daily has been shown to increase lamivudine exposure (AUG). The effect of higher doses of Co-trimoxazole on lamivudine pharmacokinetics has not been investigated. However, unless the patient has renal to impairment, no dosage adjustment of Lamivudine is necessary. Lamviudine has no effect on the pharmacokinetics of trimethoprim of sulfamethoxazole.

Zalcitabine

Lamivudine may inhibit the intracellular phosphorylation of Zalcitabine when the 2 medicinal pregnant products are used concurrently. Lamivudine150 mg and Zidovudine 300 mg Tablets is therefore not recommended to be used in combination with Zalcitabine.

Interactions Relevant to Zidovudine

Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated metabolite. Since Active substances which are primarily eliminated by hepatic metabolism especially via glucuronidation may have the potential to inhibit metabolism of Zidovudine.

Lamivudine

Co-administrationof Zidovudineresults in a 13% increase in Zidovudineexposure and a 28% increase in peak plasma levels. However,overall exposure (AUG) is not significantly altered Zidovudine has no effect on the pharmacokinetics of Lamivudine.

Phenytoin:

Phenytoin blood levels have been reported to be low in some patients receiving Zidovudine, while in 1 patient, a high level was noted. These observations suggest that phenytoin concentrations should be carefully monitored in patients receiving Lamivudine150 mg and Zidovudine 300 mg Tablets and Phenytoin.

Probenicid

Probenecid increases the mean half-life and AUG of Zidovudine by decreasing glucuronidation Renal excretion of the glucuronide (and possibly Zidovudine itself) is reduced in the presence of Probenecid.

Ribavirin:

The nucleoside analogue ribavirin antagonizes the in vitro antiviral activity of Zidovudine and so, concomitant use of Lamivudine150 mg and Zidovudine 300 mg Tablets with Ribavirin should be avoided.

Rifampicin :

Co-administration of Zidovudine and Rifampicin decreases AUG of Zidovudine by 48±34%. However the clinical significance of this is unknown

Stavudine :

Zidovudine may inhibit the intracellular phosphorylation of Stavudine when the 2 medicinalproducts are used concurrently. Stavudine is therefore not recommended to be used in combination with Lamivudine150 mg and Zidovudine 300 mg Tablets.

Others:

Other medicinal products, including but not limited to, aspirin, codeine, morphine, methadone, indomethacin, ketoprofen, naproxe,noxazepam, lorazepam, cimetidine, clofibrate, dapsone and lsoprinosnie, may alter the metabolism of Zidovudine by competitively inhibiting glucuronidation

or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibilities of interactions before using such medicinal products particularly for chronic therapy in combination with Lamivudine150 mg and Zidovudine 300 mg Tablets.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (eg, systemic pentamidin,e dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytocine, ganciclovir, interferon, vincristine, vinblastine, and doxorubicin) may also increase the risk of adverse reactions to Zidovudine.If concomitant therapy with Lamivuidne 150 mg and Zidovudine300 mg Tablets and any of these medicinal products is necessary, then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced.

USE IN PREGNANCY AND LACTATION:

Pregnancy

There are no adequate and well-controlled studies of lamivudine and zidovudine in pregnant women. The use of Zidovudine in pregnant women, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal-foetal transmission of HIV. Both Lamivudine and Zidovudine have been shown to cross the placenta. Administration of Lamivudine150 mg and Zidovudine 300 mg Tablets during the first 3 months of pregnancy is not recommended unless the benefit to the mother outweighs the risk of the foetus.

There have been reports of mild, transient elevations in serum lactate levels, which may be due mitochondrial dysfunction, in neonates and infants exposed in utero or peripartum to NRTIs. The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of development delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure in utero or peripartum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to

prevent vertical transmission of HIV.

Lactation

Health experts recommend that, where possible, HIV-infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV. Both Lamviudine and Zidovudine are excreted in human milk at similar concentrations to those found in serum. Since Lamivudine, Zidovudine and HIV virus pass into breast milk, it is recommended that mothers taking Lamivudine150 mg and Zidovudine300 mg Tablet do not breastfeed their infants.

SIDE EFFECTS

Adverse events have been reported during therapy for HIV disease with Lamivudine and Zidovudine separately or in combination. With many, it is nuclease whether they are related to Lamivudine, Zidovudine or to the wide range of medicinal products used in the management of HIV disease, or are as a result of the underlying disease process. The type and severity of adverse reactions associated with either Lamivudine or Zidovudine, may be expected. There is no evidence of added toxicity following the concurrent administration of the 2 compounds.

Lamivudine

Blood and Lymphatic Systems Disorders

Uncommon: Neutropenia, anaemia, thrombocytopenia. Very rare: Pure red cell aplasia.

Metabolism and Nutrition Disorders

Common: Hyperlactataemia. Rare: Lactic acidosis. Redistribution/accumulation of body fat.

The indicidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.

Nervous System Disorders

Common: Headache. Very Rare: Paraesthesia. Peripheral neuropathy has been reported although a causal relationship to treatment is uncertain.

Gastrointestinal Disorders

Common: Nausea, vomiting, upper abdominal pain, diarrhoea. Rare: Pancreatitis, although a causal relationship to treatment is uncertain. Rises in serum amylase.

Hepatobiliary Disorders

Uncommon: Transient rises in liver enzymes (AST, ALT). Skin and Subcutaneous Tissue Disorders

Common: Rash, alopecia

Musculoskeletal and Connective Tissue Disorders Common: Arthralgia, muscle disorders. Rare: Rhabdomyolysis General Disorders and Administration Site Conditions Common: Fatigue, malaise, fever.

Zidovudine

Blood and Lymphatic Systems Disorders

Common: Anaemia (which may require transfusions,) neutropenia and leucopenia. These occur more frequently at higher dosages (1200-1500mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment) and particularly in patients with DC4 cell counts <100/mm^3. Dosage reduction or cessation of therapy may become necessary. The incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin B_{12} levels were low at the start of Zidovudine therapy. Uncommon: Thrombocytopenia and pancytopenia (with marrow hypoplasia.) Rare: Pure red cell aplasia. Very rare : Aplastic anaemia.

Psychiatric Disorders.

Rare : Anxiety and depression. Nervous System Disorders

Very common: Headache. Common: Dizziness. Rare: Insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions

Cardiac Disorders Rare: Cardiomyopathy

Respiratory, Thoracic and Mediastinal Disorders Uncommon: Dyspnoea. Rare: Cough Gastrointestinal Disorders

Common: Vomiting, abdominal pain and diarrhoea. Uncommon: Flatulence. Rare: Oral mucosa pigmentation, taste disturbance and dyspepsia, pancreatitis.

Hepatobiliary Disorders:

Common: Raised blood levels of liver enzymes and bilirubin. Rare: Liver disorders eg, severe hepatomegaly with steatosis.

Skin and Subcutaneous Tissue Disorders

Uncommon: Rash and pruritus. Rare: Nail and skin pigmentation, urticaria and sweating. Musculoskeletal and Connective Tissue Disorders

Common: Myalgia. Uncommon: Myopathy. Renal and Urinary Disorders

Rare: Urinary frequency Reproductive System and Breast Disorders

Rare: Gynaecomastia.

General Disorders and Administration Site Conditions

Common: Malaise. Uncommon: Fever, generalized pain and asthenia. Rare: Chills, chest pain and influenza-like syndrome.

OVERDOSE AND TREATMENT

There is limited experience of overdosage with Lamviudine 150 mg and Zidovudine 300 mg Tablets. No specific signs or symptoms have been identified following acute overdose with Zidovudine or Lamivudine apart from those listed as undesirable effects. No fatalities occurred and all patients recovered.

If overdosage occurs, the patient should be monitored for evidence of toxicity and standard supportive treatment applied as necessary. Since Lamivudine is dialyzable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied. Haemodialysiasnd peritoneladialysis appear to have a limited effect on the elimination of Zidovudine, but enhance the elimination of the glucuronide metabolite. For more details, physicians should refer to the individual prescribing information for Lamivudine and Zidovudine.

STORAGE: Store below 30°C. Protect from light. Keep all medicines away from children.

AVAILABILITY: Bottle of 60 tablets.

For further information, please consult your physician or pharmacist.

Manufactured by:
Strides Pharma Science Limited
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Product Registration Holder & Imported by:
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