ZIDOVEX L (LAMIVUDINE 150 mg and ZIDOVUDINE 300 mg TABLETS)

Description:
White to off-white, modified capsule shaped, biconvex, film coated tablets, debossed with C and 60 on one side and plain on the other side.

Each tablet contains lamivudine 150mg and zidovudine 300mg.

Pharmacodynamics
Lamivudine and zidovudine are nucleoside analogues which have activity against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both medicinal products are metabolized intracellularly to their active moieties, lamivudine 5'-triphosphate (TP) and zidovudine 5'-TP respectively. Their main modes of action are as chain terminators of viral reverse transcription. Lamivudine-TP and zidovudine-TP have selective inhibitory activity against HIV-1 and HIV-2 replication in vitro; lamivudine 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.
HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both in vitro and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity in vitro. In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.
In vitro data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTI's should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTIs are available
Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine; the clinical significance of these findings is unknown. In vitro susceptibility testing has not been standardized and results may vary according to methodological factors.
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 in vitro. Resistance to thymidine analogues (of which zidovudine is one) is well characterized and is conferred by the stepwise accumulation of up to six specific mutations in the HIV reverse transcriptase at codons 41, 67, 70, 210, 215 and 219. Viruses acquire phenotypic resistance to thymidine analogues through the combination of mutations at codons 41 and 215 or by the accumulation of at least four of the six mutations. These thymidine analogue mutations alone do not cause high-level cross-resistance to any of the other nucleosides, allowing for the subsequent use of any of the other approved reverse transcriptase inhibitors.
Two patterns of multi-drug resistance mutations, the first characterized by mutations in the HIV reverse transcriptase at codons 62, 75, 77, 116 and 151 and the second involving a T69S mutation plus a 6-base pair insert at the same position, result in phenotypic resistance to AZT as well as to the other approved NRTIs. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

Pharmacokinetic

Absorption: Lamivudine and zidovudine are well absorbed from the gastrointestinal tract.

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%.

Metabolism: Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately 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 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 intravenous dosing.

Elimination: The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (>70%) via the organic cationic transport system.

Pharmacokinetics in children: In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age. Due to these differences, the recommended dose for lamivudine in children (aged more than three months and weighing less than 30 kg) is 4 mg/kg twice a day. This dose will achieve an average AUC 0-12 ranging from approximately 3,800 to 5,300 ng h/ml. Recent findings indicate that exposure in children <6 years of age may be reduced by about 30% compared with other age groups.

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

Indication

Lamivudine and zidovudine tablets are indicated in anti-retroviral combination therapy for Human Immunodeficiency Virus (HIV).

Recommended Dose

LAMIVUDINE AND ZIDOVUDINE therapy should be initiated and monitored by a physician experienced in the management of HIV infection. LAMIVUDINE AND ZIDOVUDINE may be administered with or without food. To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. For patients who are unable to swallow tablets, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see Pharmacokinetics).

Adults and adolescents weighing at least 30kg

The recommended dose of LAMIVUDINE AND ZIDOVUDINE is one tablet twice daily.

Children weighing between 21 kg and 30 kg

The recommended oral dose of LAMIVUDINE AND ZIDOVUDINE is one-half tablet taken in the morning and one whole tablet taken in the evening.

Children weighing from 14 kg to 21 kg
The recommended oral dose of LAMIVUDINE AND ZIDOVUDINE is one-half tablet taken twice daily. For children weighing less than 14 kg, lamivudine and zidovudine should be taken as separate formulations according to the prescribed dosing for these products. If a reduction in dose of LAMIVUDINE AND ZIDOVUDINE appears clinically indicated, or if one of the components of LAMIVUDINE AND ZIDOVUDINE requires reduction or discontinuation, separate preparations of lamivudine and zidovudine are available in tablets/capsules and oral solution.

Elderly
No specific data are available, however special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

Renal impairment
Dosage adjustment of lamivudine is required in patients with a creatinine clearance of less than 50 ml/min (see Pharmacokinetics). It is therefore recommended that separate preparations of lamivudine and zidovudine should be administered to these patients.

Hepatic impairment
Dosage adjustments for zidovudine may be necessary in patients with hepatic impairment (see Pharmacokinetics). It is therefore recommended that separate preparations of lamivudine and zidovudine should be administered to patients with severe hepatic impairment.

Dosage adjustments in patients with haematological adverse reactions
Dosage adjustment of zidovudine may be necessary if the haemoglobin level falls below 9 g/dl or 5.59 mmol/l or the neutrophil count falls below 1.0 x 109/l (see Contraindications and Warnings and Precautions). As dosage adjustment of LAMIVUDINE AND ZIDOVUDINE is not possible separate preparations of zidovudine and lamivudine should be used.

Mode of administration
Oral

Contraindication
Hypersensitivity to active substances or to any of the excipients.

<u>*Zidovudine*</u>
Zidovudine tablets should not be given to patients with abnormally low neutrophil counts (less than 0.75 x 10^9 /litre) or abnormally low haemoglobin levels (less than 7.5 g/decilitre or 4.65 mmol/litre).

Warning and precautions
The special warnings and precautions relevant to both lamivudine and zidovudine are included in this section. There are no additional precautions and warnings relevant to the combination LAMIVUDINE AND ZIDOVUDINE.
It is recommended that separate preparations of lamivudine and zidovudine should be administered in cases where dosage adjustment is necessary. In these cases the physician should refer to the individual prescribing information for these medicinal products.
The concomitant use of stavudine with zidovudine should be avoided.

Opportunistic infections: Patients receiving LAMIVUDINE AND ZIDOVUDINE 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 physicians experienced in the treatment of HIV infection.

Transmission of HIV: Patients should be advised that current antiretroviral therapy, including LAMIVUDINE AND ZIDOVUDINE, 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 (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) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease. Haematological parameters should therefore be carefully monitored in patients receiving LAMIVUDINE AND ZIDOVUDINE. These haematological effects are not usually observed before four to six weeks therapy. For patients with advanced symptomatic HIV disease, it is generally recommended that blood tests are performed at least every two weeks for the first three 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, for example every one to three months. Additionally dosage adjustment of zidovudine may be required if severe anaemia or myelosuppression occurs during treatment with LAMIVUDINE AND ZIDOVUDINE, or in patients with pre-existing bone marrow compromise e.g. haemoglobin <9 g/dl (5.59 mmol/l) or neutrophil count <1.0 x 10 9 /l. As dosage adjustment of LAMIVUDINE AND ZIDOVUDINE is not possible separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the individual prescribing information for these medicinal products.

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 the antiretroviral treatment or to the underlying HIV disease. Treatment with LAMIVUDINE AND ZIDOVUDINE should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Lactic acidosis: lactic acidosis usually associated with hepatomegaly and hepatic steatosis has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain) non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued if there is symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.
Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.
Patients at increased risk should be followed closely.

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 post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological

disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations 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. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis jiroveci pneumonia (*formerly known as *Pneumocystis carinii pneumonia)*. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Liver disease: If lamivudine is being used concomitantly for the treatment of HIV and HBV, additional information relating to the use of lamivudine in the treatment of hepatitis B infection is available in the Zeffix SmPC.

The safety and efficacy of zidovudine has not been established in patients with significant underlying liver disorders.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

If LAMIVUDINE AND ZIDOVUDINE is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication for 4 months is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients co-infected with hepatitis C virus: The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia.

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 antiretroviral therapy (CART). Patients should be advised to LAMIVUDINE AND ZIDOVUDINEk medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

LAMIVUDINE AND ZIDOVUDINE should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

Interactions with Other Medicaments

Lamivudine

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

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 e.g. trimethoprim. Other active substances (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

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

Zidovudine: A modest increase in C_{max} (28%) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine had no effect on the pharmacokinetics of lamivudine.

Trimethoprim/sulphamethoxazole: Administration of trimethoprim/sulphamethoxazole 160mg/800mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effects on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole for the treatment of *Pneumocystis jiroveci (P.carinii)* pneumonia and toxoplasmosis has not been studied.

Zalcitabine: Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine.

Zidovudine

Limited data suggests that co-administration of zidovudine with rifampicin decreases the AUC (area under the plasma concentration curve) of zidovudine by 48% ± 34%. This may result in a partial loss or total loss of efficacy of zidovudine.

Zidovudine in combination with either ribavirin or stavudine are antagonistic in vitro. The concomitant use of either ribavirin or stavudine with zidovudine should be avoided.

Probenecid increases the AUC of zidovudine by 106% (range 100 to 170%). Patients receiving both drugs should be closely monitored for haematological toxicity.

A modest increase in C_{max} (28%) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Phenytoin blood levels have been reported to be low in some patients receiving zidovudine tablets, while in one patient a high level was noted. These observations suggest that phenytoin levels should be carefully monitored in patients receiving both drugs.

In a pharmacokinetic study co-administration of zidovudine and atovaquone showed a decrease in zidovudine clearance after oral dosing leading to a 35%±23% increase in plasma zidovudine AUC. Given the limited data available the clinical significance of this is unknown.

Valproic acid, fluconazole or methadone when co-administered with zidovudine have been shown to increase the AUC with a corresponding decrease in its clearance. As only limited data are available the clinical significance of these findings is unclear but if zidovudine is used concurrently with either

valproic acid, fluconazole or methadone, patients should be monitored closely for potential toxicity of zidovudine.
Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive drugs (eg. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, 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 dosage of one or more agents should be reduced.
Since some patients receiving zidovudine may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Such prophylaxis has included co-trimoxazole, aerosolised pentamidine, pyrimethamine and aciclovir. Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with these drugs at doses used in prophylaxis. Clarithromycin tablets reduce the absorption of Zidovudine.

Pregnancy and Lactation
Pregnancy: As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account. In the present case, the use in pregnant women of zidovudine, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal-foetal transmission of HIV. A large amount of data on pregnant women taking lamivudine or zidovudine indicate no malformative toxicity (more than 3000 outcomes from first trimester exposure each, of which over 2000 outcomes involved exposure to both lamivudine and zidovudine). The malformative risk is unlikely in humans based on the mentioned large amount of data

The active ingredients of LAMIVUDINE AND ZIDOVUDINE may inhibit cellular DNA replication and zidovudine has been shown to be transplacental carcinogen in one animal study. The clinical relevance of these findings is unknown.

For patients co-infected with hepatitis who are being treated with lamivudine containing medicinal products such as LAMIVUDINE AND ZIDOVUDINE and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

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 post-natally to nucleoside analogues.

Breastfeeding: Both lamivudine and zidovudine are excreted in breast milk at similar concentrations to those found in serum. As a general rule, it is recommended that mothers infected by HIV do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility: Neither zidovudine nor lamivudine have shown evidence of impairment of fertility in studies in male and female rats. There are no data on their affect on human female fertility.

In men zidovudine has not been shown to affect sperm count, morphology or motility.

Side effects
Adverse reactions have been reported during therapy for HIV disease with lamivudine and zidovudine separately or in combination. For many of these events, it is unclear whether they are related to lamivudine, zidovudine, the wide range of medicinal products used in the management of HIV disease, or as a result of the underlying disease process.

As LAMIVUDINE AND ZIDOVUDINE 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 concurrent administration of the two compounds.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues.
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).
Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown.

Lamivudine:
The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common, common, uncommon, rare, very rare. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic systems disorders
Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia
Very rare: Pure red cell aplasia

Nervous system disorders
Common: Headache, insomnia
Very rare: Peripheral neuropathy (or paraesthesiae)

Respiratory, thoracic and mediastinal disorders
Common: Cough, nasal symptoms

Gastrointestinal disorders
Common: Nausea, vomiting, abdominal pain or cramps, diarrhoea
Rare: Pancreatitis, rises in serum amylase

Hepatobiliary disorders
Uncommon: Transient rises in liver enzymes (AST, ALT)
Rare: Hepatitis

Skin and subcutaneous tissue disorders
Common: Rash, alopecia
Rare: Angioedema

Musculoskeletal and connective tissue disorders
Common: Arthralgia, muscle disorders

Rare: Rhabdomyolysis

General disorders and administration site conditions
Common: Fatigue, malaise, fever

Zidovudine:
The adverse reactions profile appears similar for adults and adolescents. The most serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia. These occurred more frequently at higher dosages (1200-1500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4 cell counts less than 100/mm 3.

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.

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common, common, uncommon, rare, very rare. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
Common: Anaemia, neutropenia and leucopenia
Uncommon: Thrombocyopenia and pancytopenia (with marrow hypoplasia)
Rare: Pure red cell aplasia
Very rare: Aplastic anaemia

Metabolism and nutrition disorders
Rare: Lactic acidosis in the absence of hypoxaemia, anorexia

Psychiatric disorders
Rare: Anxiety and depression

Nervous system disorders
Very common: Headache
Common: Dizziness
Rare: Insomnia, paraesthesiae, somnolence, loss of mental acuity, convulsions

Cardiac disorders
Rare: Cardiomyopathy

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea
Rare: Cough

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting, abdominal pain and diarrhoea
Uncommon: Flatulence
Rare: Oral mucosa pigmentation, taste perversion and dyspepsia. Pancreatitis

Hepatobiliary disorders
Common: Raised blood levels of liver enzymes and bilirubin

Rare: Liver disorders such as 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, generalised pain and asthenia
Rare: Chills, chest pain and influenza-like syndrome

The available data from both placebo-controlled and open-label studies indicate that the incidence of nausea and other frequently reported clinical adverse events consistently decreases over time during the first few weeks of therapy with zidovudine.

Symptoms and Treatment of Overdose
Lamivudine
Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.
If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

Zidovudine
No specific symptoms or signs have been identified following acute overdose with zidovudine apart from those listed as undesirable effects such as fatigue, headache, vomiting, and occasional reports of haematological disturbances. Following a report where a patient took an unspecified quantity of zidovudine with serum levels consistent with an overdose of greater than 17 grams there were no short term clinical, biochemical or haematological sequelae identified.

Storage Condition
Do not store above 30°C. Keep the container tightly closed. Store in the original package.

Shelf Life
36 months

Presentation
60's tablets are packed in white 110 mL HDPE container closed with cap containing induction sealing wad.

Manufactured by:
Aurobindo Pharma Limited (Unit-III),
Survey No.313,314 Bachupally,
Bachupally Mandal, Medchal-
Malkajgiri Dist,
Telangana State, India.

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