SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lamivudine/Zidovudine 150 mg/300 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lamivudine 150 mg and zidovudine 300 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white modified capsule-shaped, biconvex film-coated tablets with deep break line in between 'J' and '59 on one side and break line on other side. The tablet can be divided into equal doses. The size is 17.2 mm X 8.15 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lamivudine/Zidovudine is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection (see section 4.2).

4.2 Posology and method of administration

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

Lamivudine/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, tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see section 5.2).

Adults and adolescents weighing at least 30 kg:

The recommended dose of Lamivudine/Zidovudine is one tablet twice daily.

Children weighing between 21 kg and 30 kg:

The recommended oral dose of Lamivudine/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/Zidovudine is one-half tablet taken twice daily.

The dosing regimen for paediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling and supported by data from clinical studies using the individual components lamivudine and zidovudine. A pharmacokinetic overexposure of zidovudine can occur, therefore close safety monitoring is warranted in these patients. If gastrointestinal intolerance occurs in patients weighing 21-30 kg, an alternative dosing schedule with one-half tablet taken thrice daily can be applied in attempt to improve tolerability.

Lamivudine/Zidovudine tablets should not be used for children weighing less than 14 kg, since doses can not be appropriately adjusted for the weight of the child. In these patients, lamivudine and zidovudine should be taken as separate formulations according to the prescribed dosing recommendations for these products. For these patients and for patients, who are unable to swallow tablets, oral solutions of lamivudine and zidovudine are available.

For situations where discontinuation of therapy with one of the active substances of Lamivudine/Zidovudine, or dose reduction is necessary separate preparations of lamivudine and zidovudine are available in tablets/capsules and oral solution.

*Renal impairment***:** Lamivudine and zidovudine concentrations are increased in patients with renal impairment due to decreased clearance (see section 4.4). Therefore as dosage adjustment of these may be necessary it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with severe renal impairment (creatinine clearance ≤ 30 mL/min). Physicians should refer to the individual prescribing information for these medicinal products.

Hepatic impairment: Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment

because of decreased glucuronidation. Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. However, as dosage adjustments for zidovudine may be necessary, it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with severe hepatic impairment. Physicians should refer to the individual prescribing information for these medicinal products.

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 10^9/L (see sections 4.3 and 4.4). As dosage adjustment of Lamivudine/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.

Dosage in the 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.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Zidovudine is contraindicated in patients with abnormally low neutrophil counts (<0.75 x 10^9/l), or abnormally low haemoglobin levels (<7.5 g/dL or 4.65 mmol/L). Lamivudine/Zidovudine is therefore contraindicated in these patients (see section 4.4).

4.4 Special warnings and precautions for use

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/Zidovudine.

It is recommended that separate preparations of lamivudine and zidovudine should be administered in cases where dosage adjustment is necessary (see section 4.2). 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 (see section 4.5).

Opportunistic infections

Patients receiving Lamivudine/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.

Haematological adverse reactions

Anaemia, neutropenia and leukopenia (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 (see section 4.3) in patients receiving Lamivudine/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/Zidovudine, or in patients with pre-existing bone marrow compromise e.g. haemoglobin <9 g/dL (5.59 mmol/L) or neutrophil count $<1.0 \times 10^9$/L (see section 4.2). As dosage adjustment of Lamivudine/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/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 zidovudine. 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 zidovudine 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 zidovudine 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 following exposure in utero

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown etiology particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lipoatrophy

Treatment with zidovudine has been associated with loss of subcutaneous fat, which has been linked to mitochondrial toxicity. The incidence and severity of lipoatrophy are related to cumulative exposure. This fat loss, which is most evident in the face, limbs and buttocks, may not be reversible when switching to a zidovudine-free regimen. Patients should be regularly assessed for signs of lipoatrophy during therapy with zidovudine and zidovudine-containing products (Lamivudine/Zidovudine and Lamivudine/Zidovudine/Abacavir). Therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy development.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. 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 (often referred to as PCP).*Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Liver disease

If lamivudine is being used concomitantly for the treatment of HIV and hepatitis B virus (HBV), additional information relating to the use of lamivudine in the treatment of hepatitis B infection is available in the Lamivudine 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/Zidovudine is discontinued in patients co-infected with HBV, 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 (see section 4.5).

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 seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Lamivudine/Zidovudine should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

The combination of lamivudine with cladribine is not recommended (see section 4.5).

Administration in subjects with moderate renal impairment

Patients with a creatinine clearance between 30 and 49 mL/min receiving Lamivudine/Zidovudine may experience a 1.6-to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL/min. There are no safety data from randomized, controlled trials comparing Lamivudine/Zidovudine to the individual components in patients with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of haematologic toxicities (neutropenia and anaemia), although discontinuations due to neutropenia or anaemia each occurred in <1% of subjects. Other lamivudine related adverse events (such as gastro-intestinal and hepatic disorders) may occur.

Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive Lamivudine/Zidovudine should be monitored for lamivudine-related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, per lamivudine prescribing information, is indicated, which cannot be achieved with Lamivudine/Zidovudine. Lamivudine/Zidovudine should be discontinued and the individual components should be used to construct the treatment regimen.

Excipients

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Lamivudine/Zidovudine contains lamivudine and zidovudine, therefore any interactions identified for these individually are relevant to Lamivudine/Zidovudine. Clinical studies have shown that there are no clinically significant interactions between lamivudine and zidovudine.

Zidovudine is primarily metabolised by UGT enzymes; co-administration of inducers or inhibitors of UGT enzymes could alter zidovudine exposure. Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through organic cation transporters (OCTs); co-administration of lamivudine with OCT inhibitors or nephrotoxic drugs may increase lamivudine exposure.

Lamivudine and zidovudine are not significantly metabolised by cytochrome P_{450} enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6) nor do they 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 P_{450} enzymes.

Interaction studies have only been performed in adults. The list below should not be considered exhaustive but is representative of the classes studied.

Drugs by Therapeutic Area	**Interaction Geometric mean change (%) (Possible mechanism)**	**Recommendation concerning co-administration**
ANTIRETROVIRAL MEDICINAL PRODUCTS		
Didanosine/Lamivudine	Interaction not studied.	No dosage adjustment necessary
Didanosine /Zidovudine	Interaction not studied.	
Stavudine/Lamivudine	Interaction not studied.	Combination not recommended.
Stavudine/Zidovudine	In vitro antagonism of anti-HIV activity between stavudine and zidovudine could result in decreased efficacy of both drugs.	
ANTI-INFECTIVE PRODUCTS		
Atovaquone/Lamivudine	Interaction not studied.	As only limited data available the clinical significance is unknown.
Atovaquone/Zidovudine (750 mg twice daily with food/200 mg thrice daily)	Zidovudine AUC ↑33% Atovaquone AUC ↔	
Clarithromycin/Lamivudine	Interaction not studied.	Separate administration of Lamivudine/Zidovudine and clarithromycin by at
Clarithromycin/Zidovudine (500 mg twice daily/100 mg every 4 hours)	Zidovudine AUC ↓12%	

		least 2 hours
Trimethoprim/sulfamethoxazole (Co- trimoxazole) /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 Lamivudine/Zidovudine dosage adjustment necessary, unless patient has renal impairment (See Section 4.2). When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim/ sulfamethoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided.
Trimethoprim/sulfamethoxazole (Co-trimoxazole) /Zidovudine	Interaction not studied.	
ANTIFUNGALS		
Fluconazole/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
Fluconazole/Zidovudine (400 mg once daily/200 mg thrice daily)	Zidovudine AUC ↑74% (UGT inhibition)	
ANTIMYCOBACTERIALS		
Rifampicin/Lamivudine	Interaction not studied.	Insufficient data to recommend dosage adjustment.
Rifampicin/Zidovudine (600 mg once daily/200 mg thrice daily)	Zidovudine AUC ↓48% (UGT induction)	
ANTICONVULSANTS		
Phenobarbital/Lamivudine	Interaction not studied.	Insufficient data to recommend dosage adjustment.
Phenobarbital/Zidovudine	Interaction not studied. Potential to slightly decrease zidovudine plasma concentrations through UGT induction.	
Phenytoin/Lamivudine	Interaction not studied.	Monitor phenytoin concentrations.
Phenytoin/Zidovudine	Phenytoin AUC ↑↓	
Valproic acid/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine
Valproic acid/Zidovudine (250 mg or 500 mg thrice daily/100 mg thrice daily)	Zidovudine AUC ↑80% (UGT inhibition)	

		toxicity (see section 4.8).
ANTIHISTAMINES (HISTAMINE H1 RECEPTOR ANTAGONISTS)		
Ranitidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Ranitidine eliminated only in part by renal organic cation transport system.	No dosage adjustment necessary.
Ranitidine/Zidovudine	Interaction not studied	
Cimetidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Cimetidine eliminated only in part by renal organic cation transport system.	No dosage adjustment necessary.
Cimetidine/Zidovudine	Interaction not studied.	
CYTOTOXICS		
Cladribine/Lamivudine	Interaction not studied *In vitro* lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine	Therefore the concomitant use of lamivudine with cladribine is not recommended (see section 4.4)
OPIOIDS		
Methadone/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8). Methadone dosage adjustment unlikely in majority of patients; occasionally methadone re-titration may be required.
Methadone/Zidovudine (30 to 90 mg once daily/200 mg every 4 hours)	Zidovudine AUC ↑43% Methadone AUC ↔	
URICOSURIC		

Probenecid/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
Probenecid/Zidovudine (500 mg four times daily/2mg/kg thrice daily)	Zidovudine AUC ↑106% (UGT inhibition)	
MISCELLANEOUS		
Sorbitol solution (3.2g , 10.2 g, 13.4 g)/ Lamivudine	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14%; 32%; 36% Cmax ↓ 28%; 52%, 55%.	When possible, avoid chronic coadministration of Lamivudine/ Zidovudine with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

Abbreviations: ↑ = Increase; ↓=decrease; ↔= no significant change; AUC=area under the concentration versus time curve; Cmax=maximum observed concentration; CL/F=apparent oral clearance

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (e.g. 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 Lamivudine/Zidovudine 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.

Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole (see interaction

information above relating to lamivudine and co-trimoxazole), aerosolised pentamidine, pyrimethamine and acyclovir at doses used in prophylaxis.

4.6 Fertility, 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/Zidovudine may inhibit cellular DNA replication and zidovudine has been shown to be transplacental carcinogen in one animal study (see section 5.3). 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/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 (see section 4.4).

Breast-feeding

Both lamivudine and zidovudine are excreted in breast milk at similar concentrations to those found in serum.

Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age.

There are no data available on the safety of lamivudine when administered to babies less than three months old.
After administration of a single dose of 200 mg zidovudine to HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

It is recommended that women living with HIV do not breast-feed their infants 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 effect on human female fertility.
In men zidovudine has not been shown to affect sperm count, morphology or motility.

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.

4.8 Undesirable 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/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 zidovudine (see section 4.4).

Treatment with zidovudine has been associated with loss of subcutaneous fat which is most evident in the face, limbs and buttocks. Patients receiving Lamivudine/Zidovudine should be frequently examined and questioned for signs of lipoatrophy. When such development is found, treatment with Lamivudine/Zidovudine should not be continued (see section 4.4).

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

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. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000). 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

Metabolism and nutrition disorders

Very Rare: Lactic acidosis

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 leukopenia. 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 $100/mm^3$ (see section 4.4).

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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Common: Anaemia, neutropenia and leukopenia

Uncommon: Thrombocytopenia 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is limited experience of overdosage with Lamivudine/Zidovudine. No specific symptoms or signs have been identified following acute overdose with zidovudine or lamivudine apart from those listed as undesirable effects.

If overdosage occurs the patient should be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

Haemodialysis and peritoneal dialysis appear to have a limited effect on 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Lamivudine and zidovudine are nucleoside analogues which 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'-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. No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine and nevirapine). No antagonistic effects in vitro were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine and interferon-alpha).
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 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, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible nucleoside analogue reverse-transcriptase inhibitors (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 standardised 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 characterised 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 characterised 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.

Clinical Experience

In clinical trials, lamivudine in combination with zidovudine has been shown to reduce HIV-1 viral load and increase 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.

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, nonnucleoside reverse transcriptase inhibitors).

Multiple drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretroviral-naive patients as well as in patients presenting with viruses containing the M184V mutations.

Evidence from clinical studies shows that lamivudine plus zidovudine delays the emergence of zidovudine resistant isolates in individuals with no prior antiretroviral therapy. Subjects receiving lamivudine and zidovudine with or without additional concomitant antiretroviral therapies and who already present with the M184V mutant virus also experience a delay in the onset of

mutations that confer resistance to zidovudine and stavudine (Thymidine Analogue Mutations; TAMs).

The relationship between *in vitro* susceptibility of HIV to lamivudine and zidovudine and clinical response to lamivudine/zidovudine containing therapy remains under investigation.

Lamivudine at a dose of 100 mg once daily has also been shown to be effective for the treatment of adult patients with chronic HBV infection (for details of clinical studies, see the prescribing information for lamivudine). However, for the treatment of HIV infection only a 300 mg daily dose of lamivudine (in combination with other antiretroviral agents) has been shown to be efficacious.

Lamivudine 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%.

A bioequivalence study compared Lamivudine/Zidovudine with lamivudine 150 mg and zidovudine 300 mg tablets taken together. The effect of food on the rate and extent of absorption was also studied. Lamivudine/Zidovudine was shown to be bioequivalent to lamivudine 150 mg and zidovudine 300 mg given as separate tablets, when administered to fasting subjects.

Following single dose Lamivudine/Zidovudine administration in healthy volunteers, mean (CV) lamivudine and zidovudine C_{max} values were 1.6 µg/ml (32%) and 2.0 µg/ml (40%), respectively and the corresponding values for AUC were 6.1 µg h/ml (20%) and 2.4 µg h/ml (29%) respectively. The median (range) lamivudine and zidovudine t_{max} values were 0.75 (0.50-2.00) hours and 0.50 (0.25-2.00) hours respectively. The extent of lamivudine and zidovudine absorption (AUC_{∞}) and estimates of half-life following administration of Lamivudine/Zidovudine with food were similar when compared to fasting subjects, although the rates of absorption (C_{max}, t_{max}) were slowed. Based on these data Lamivudine/Zidovudine may be administered with or without food.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on 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 crushes and transfers 100% of the tablet and ingests immediately.

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%. Interactions involving binding site displacement are not anticipated with Lamivudine/Zidovudine.

Data show that lamivudine and zidovudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). The mean ratios of CSF/serum lamivudine and zidovudine concentrations 2-4 hours after oral administration were approximately 0.12 and 0.5 respectively. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Biotransformation:

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 18 to 19 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. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance ≤ 30 ml/min (see section 4.2).

From 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. 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 children: 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% with a mean of 65%. Css_{max} levels were 4.45 μM (1.19 μg/ml) following a dose of 120 mg zidovudine (in solution)/m^2 body surface area and 7.7 μM (2.06 μg/ml) at 180 mg/m^2 body surface area. Dosages of 180 mg/m^2 four times daily in children produced similar systemic exposure (24 hour AUC 40.0 h μM or 10.7 h μg/ml) as doses of 200 mg six times daily in adults (40.7 h μM or 10.9 h μg/ml).

In six HIV-infected children from 2 to 13 years of age, zidovudine plasma pharmacokinetics were evaluated while subjects were receiving 120 mg/m^2 zidovudine three times daily and again after switching to 180 mg/m^2 twice daily. Systemic exposures (daily AUC and C_{max}) in plasma from the twice daily regimen appeared equivalent to those from the same total daily dose given in three divided doses [Bergshoeff, 2004].

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. Further data addressing this issue are currently awaited. At present, the available data do not suggest that lamivudine is less efficacious in this age group.

Pharmacokinetics in pregnancy

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

5.3 Preclinical safety data

The clinically relevant effects of lamivudine and zidovudine in combination are anaemia, neutropenia and leukopenia.

Mutagenicity and carcinogenicity

Neither lamivudine nor zidovudine are mutagenic in bacterial tests, but consistent with other nucleoside analogues, inhibit cellular DNA replication 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. Peripheral blood lymphocytes from AIDS patients receiving zidovudine treatment have also been observed to contain higher numbers of chromosome breakages.

A pilot study has demonstrated that zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The 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 long-term 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, by the US National Cancer Institute, 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.

While the clinical relevance of these findings is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

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

Tablet core:

Cellulose microcrystalline

Sodium starch glycolate (Type A)

Silica colloidal anhydrous

Magnesium stearate

Tablet coat:

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol 400

Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Lamivudine/Zidovudine film-coated tablets are available in PVC/PVdC-Aluminium foil blisters and HDPE bottle with polypropylene closures. Pack sizes:

Blister pack: 60 & 180 film-coated tablets

HDPE pack: 60 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handlings

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited

Ares Block, Odyssey Business Park

West End Road

Ruislip HA4 6QD

United Kingdom

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