COMBIVIR

Lamivudine-Zidovudine

QUALITATIVE AND QUANTITATIVE COMPOSITION

COMBIVIR tablets contain 150 mg lamivudine and 300 mg zidovudine and are white to off-white capsule-shaped, scored tablets, engraved with GX FC3 on both faces.

CLINICAL INFORMATION

Indications

COMBIVIR is indicated for the treatment of HIV infection.

Dosage and Administration

Pharmaceutical Form: Film-coated tablets.

COMBIVIR therapy should be initiated and monitored by a physician experienced in the management of HIV infection.

COMBIVIR 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, they may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (*see Pharmacokinetics*).

Populations

- **Adults and adolescents weighing at least 30 kg:**

The recommended dose of *COMBIVIR* is one tablet twice daily.

- **Children weighing between 21 kg and 30 kg**

The recommended oral dose of *COMBIVIR* 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 *COMBIVIR* is one-half tablet taken twice daily.

For children weighing less than 14 kg, lamivudine (*EPIVIR*) and zidovudine (*RETROVIR*) should be taken as separate formulations according to the prescribed dosing for these products.

If a reduction in dose of *COMBIVIR* appears clinically indicated, or if one of the components of *COMBIVIR* (lamivudine or zidovudine) requires reduction or discontinuation, separate preparations of lamivudine (*EPIVIR*) and zidovudine (*RETROVIR*) 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 30 mL/min (*see Pharmacokinetics and Warnings and Precautions*). 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 1.0×10^9/L (*see Contraindications and Warnings and Precautions*). As dosage adjustment of *COMBIVIR* is not possible separate preparations of zidovudine and lamivudine should be used.

Contraindications

The use of *COMBIVIR* is contraindicated in patients with known hypersensitivity to lamivudine, zidovudine or to any ingredient of the preparation.

Zidovudine is contraindicated in patients with abnormally low neutrophil counts (less than 0.75×10^9 /L), or abnormally low haemoglobin levels (less than 7.5 g/dL or 4.65 mmol/L). *COMBIVIR* is therefore contraindicated in these patients (*see Warnings and Precautions*).

Warnings and Precautions

The warnings and precautions relevant to both lamivudine and zidovudine are included in this section. There are no additional precautions or warnings relevant to the combination *COMBIVIR*.

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.

Patients should be cautioned about the concomitant use of self-administered medications (*see Interactions*).

- **Opportunistic infections**

Patients treated with *COMBIVIR* 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 leucopenia (usually secondary to neutropenia) can be expected to occur in patients receiving zidovudine. These occurred more frequently at higher zidovudine dosages (1200 to 1500 mg/day), in patients with advanced HIV disease and in those who had poor marrow reserve prior to treatment (*see Adverse Reactions*). Haematological parameters should therefore be carefully monitored (*see Contraindications*) in patients receiving *COMBIVIR*.

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 *COMBIVIR*, or in patients with pre-existing bone marrow compromise for example haemoglobin less than 9 g/dL (5.59 mmol/L) or neutrophil count less than 1.0×10^9 /L. As dosage adjustment of *COMBIVIR* is not possible separate preparations of zidovudine and lamivudine should be used (*see Contraindications*).

- **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 products 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 *COMBIVIR* 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 either 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 generalised weakness, anorexia and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

Caution should be exercised when administering *COMBIVIR*, particularly to those with known risk factors for liver disease. Treatment with *COMBIVIR* should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

- **Lipoatrophy**

Treatment with zidovudine has been associated with loss of subcutaneous fat. 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 be only partially reversible and improvement may take several months when switching to a zidovudine-free regimen. Patients should be regularly assessed for signs of lipoatrophy during therapy with *COMBIVIR* and other zidovudine containing products (Retrovir and Trizivir), and if feasible therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy development.

- **Serum lipids and blood glucose**

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and lifestyle changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

- **Immune Reconstitution Syndrome**

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), 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 first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia (often referred to as PCP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the

setting of immune reconstitution, however the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

- **Patients co-infected with Hepatitis B virus**

Clinical trial and marketed use of lamivudine have shown that 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 *COMBIVIR* is discontinued in patients co-infected with Hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

- **Patients co-infected with hepatitis C virus**

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. Therefore, the co-administration of ribavirin and zidovudine is not advised, and 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.

- **Patients with moderate renal impairment**

Haematological parameters should be carefully monitored in patients receiving *COMBIVIR*, including in patients with a sustained creatinine clearance between 30 and 49 mL/min. If new or worsening neutropenia or anaemia develop, a dose adjustment of zidovudine may be necessary. If a dose adjustment is needed, *COMBIVIR* should therefore be discontinued and the individual components should be used to construct the treatment regimen.

Interactions

As *COMBIVIR* contains lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur with *COMBIVIR*. The interactions listed below should not be considered exhaustive but are representative of the classes of medicinal products where caution should be exercised.

Effect of lamivudine on the pharmacokinetics of other agents

In vitro, lamivudine demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or P-glycoprotein (Pgp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K or organic cation transporter 3 (OCT3). Lamivudine is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Lamivudine is an inhibitor of OCT1 and OCT2 in vitro with IC50 values of 17 and 33 uM, respectively, however lamivudine has low potential to affect the plasma

concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg).

Effect of other agents on the pharmacokinetics of lamivudine

Lamivudine is a substrate of MATE1, MATE2-K and OCT2 in vitro. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations, however this interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Lamivudine is a substrate of Pgp and BCRP, however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, co-administration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Interactions 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 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 predominantly excreted either via the active organic anionic pathway or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.

Sorbitol: Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC_{∞}) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults. When possible, avoid chronic coadministration of sorbitol-containing medicines with *COMBIVIR*. Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

Trimethoprim: Administration of trimethoprim-sulphamethoxazole 160 mg/800 mg (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 effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with

higher doses of co-trimoxazole used for the treatment of *Pneumocystis jiroveci* pneumonia and toxoplasmosis has not been studied.

Emtricitabine: Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited. *COMBIVIR* is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.

Interactions relevant to zidovudine:

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

Atovaquone: Zidovudine does not appear to affect the pharmacokinetics of atovaquone. However, pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC of zidovudine was increased by 33% and peak plasma concentration of the glucuronide was decreased by 19%). At zidovudine dosages of 500 or 600 mg/day it would seem unlikely that a three week, concomitant course of atovaquone for the treatment of acute *Pneumocystis jiroveci* pneumonia would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine. Extra care should be taken in monitoring patients receiving prolonged atovaquone therapy.

Clarithromycin: Clarithromycin tablets reduce the absorption of zidovudine. This can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.

Lamivudine: Co-administration of zidovudine with lamivudine results in a 13% increase in zidovudine exposure and a 28% increase in peak plasma levels. However overall exposure (AUC) 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 one patient a high level was noted. These observations suggest that phenytoin concentrations should be carefully monitored in patients receiving *COMBIVIR* and phenytoin.

Probenecid: Limited data suggest that probenecid increases the mean half-life and AUC of zidovudine by decreasing glucuronidation. Renal excretion of the glucuronide (and possibly zidovudine itself) is reduced in the presence of probenecid.

Rifampicin: Limited data suggests that co-administration of zidovudine and rifampicin decreases AUC of zidovudine by 48% ± 34%. However, the clinical significance of this is unknown.

Stavudine: Zidovudine may inhibit the intracellular phosphorylation of stavudine when the two medicinal products are used concurrently. Stavudine is therefore not recommended to be used in combination with *COMBIVIR*.

Miscellaneous: Other medicinal products, including but not limited to, aspirin, codeine, morphine, methadone, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and isoprinosine, 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 *COMBIVIR*.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (for example 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 *COMBIVIR* 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.

Since some patients receiving *COMBIVIR* 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 medicinal products.

Pregnancy and Lactation

Fertility

There are no data on the effect of lamivudine or zidovudine on human female fertility. In men, zidovudine has been shown to have no effect on sperm count, morphology or motility.

Pregnancy

Lamivudine and zidovudine have been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 11,000, and 13,000 women respectively during pregnancy and postpartum. Available human data from the APR do not show an increased risk of major birth defects for lamivudine or zidovudine compared to the background rate *(see Clinical Studies).*

The safe use of lamivudine and zidovudine in human pregnancy has not been established in adequate and well-controlled trials investigating congenital abnormalities. Therefore, administration of *COMBIVIR* in pregnancy should be considered only if the expected benefit outweighs the possible risk to the foetus.

Lamivudine and zidovudine have been shown to cross the placenta in humans *(see Pharmacokinetics).*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.

Lamivudine and zidovudine have been associated with findings in animal reproductive studies (*see Non-Clinical Information).* Pregnant women considering using *COMBIVIR* during pregnancy should be made aware of these findings.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed in utero or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure in utero or peri-partum 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 in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

In a study following repeat oral dose of either 150 mg lamivudine twice daily (given in combination with 300 mg zidovudine twice daily) or 300 mg lamivudine twice daily, lamivudine was excreted in human breast milk (0.5 to 8.2 μg/mL) at similar concentrations to those found in serum, while 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. In other studies following repeat oral administration of 150 mg lamivudine (given either in combination with 300 mg zidovudine or as Combivir or Trizivir) and 300 mg zidovudine twice daily (given either as a single entity or as Combivir or Trizivir) the maternal plasma:breast milk ratio ranged between 0.4 and 3.2 for zidovudine, and 0.6 and 3.3 for lamivudine. Lamivudine median infant serum concentrations ranged between 18 and 28 ng/mL and were not detectable in one of the studies (assay sensitivity 7 ng/mL). Zidovudine median infant serum concentration was 24 ng/mL in one study and was below assay limit of qualification (30 ng/mL) in another study. Intracellular zidovudine and lamivudine triphosphate (active metabolites of zidovudine and lamivudine) levels in breastfed infants were not measured therefore the clinical relevance of the serum concentrations of the parent compounds measured is unknown.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of lamivudine or zidovudine 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.

Adverse Reactions

Adverse events have been reported during therapy for HIV disease with lamivudine and zidovudine separately or in combination. With many it is unclear 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. As *COMBIVIR* contains lamivudine and zidovudine the type and severity of adverse reactions associated with each of the compounds, which are listed below may be expected. There is no evidence of added toxicity following concurrent administration of the two compounds.

The following convention has been utilised for the classification of undesirable effects:- Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000) very rare (<1/10,000).

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 (*see Warnings and Precautions*).

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 system disorders

Common: Anaemia (which may require transfusions), neutropenia and leucopenia

These occur more frequently at higher dosages (1200 to 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. Dosage reduction or cessation of therapy may become necessary (*see Warnings and Precautions*). 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.

Metabolism and nutrition disorders

Common: Hyperlactataemia.

Rare: Lactic acidosis (*see Warnings and Precautions*), anorexia.

Treatment with zidovudine has been associated with loss of subcutaneous fat *(see Warnings and Precautions).*

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

Very common: Nausea.

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 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.

Overdose

Symptoms and Signs

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

Treatment

If overdosage occurs the patient should be monitored for evidence of toxicity (*see Adverse Reactions*), 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

Pharmacotherapeutic group - nucleoside analogue, ATC Code: J05 A F30.

Mechanism of Action

Lamivudine and zidovudine are potent, selective inhibitors of HIV-1 and HIV-2. Both active substances are metabolised sequentially by intracellular kinases to the 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 triphosphate form into the viral DNA chain, resulting in chain termination. Lamivudine and zidovudine triphosphates show significantly less affinity for host cell DNA polymerases. No antagonistic effects in vitro were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine). No antagonistic effects in vitro were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine, lamivudine and interferon-alpha).

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 *in vitro*. Lamivudine therefore has, *in vitro*, a high therapeutic index.

Pharmacodynamic Effects

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.

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 less than 4-fold decrease in susceptibility to didanosine and zalcitabine; the clinical significance of these findings is unknown.

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 typically involving a T69S mutation plus a 6-base pair insert at the same position, result in phenotypic resistance to zidovudine as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

In clinical studies lamivudine in combination with zidovudine has been shown to reduce HIV-1 viral load and to increase CD4 cell counts. Clinical end-point 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-resistant isolates in individuals with no prior anti-retroviral therapy.

In vitro susceptibility testing has not been standardised and results may vary according to methodological factors. The relationship between *in vitro* susceptibility of HIV to

lamivudine and/or zidovudine and the clinical response to therapy remain under investigation.

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 antiretroviral-naive patients as well as in patients presenting with viruses containing the M184V mutations.

Post-exposure prophylaxis (PEP):

Internationally recognised guidelines (Centre for Disease Control and Prevention - June 1998), recommend that in the event of accidental exposure to HIV infected blood e.g. from a needlestick injury, a combination of zidovudine and lamivudine should be administered promptly (within one to two hours). In cases of higher risk of infection a protease inhibitor should be included in the regimen. It is recommended that antiretroviral prophylaxis be continued for four weeks. No controlled clinical studies have been carried out in post-exposure prophylaxis and supporting data is limited. Seroconversion may still occur despite prompt treatment with antiretroviral agents.

Pharmacokinetics

Absorption

Lamivudine and zidovudine are well absorbed from the gut. The bioavailability of oral lamivudine in adults is normally between 80 to 85% and for zidovudine 60 to 70%. A bioequivalence study compared *COMBIVIR* with *EPIVIR* 150 mg and *RETROVIR* 300 mg tablets taken together. The effect of food on the rate and extent of absorption was also studied. *COMBIVIR* was shown to be bioequivalent to *EPIVIR* 150 mg and *RETROVIR* 300 mg given as separate tablets, when administered to fasting subjects.

Following *COMBIVIR* administration, lamivudine and zidovudine C_{max} (95% confidence interval) values were 1.5 (1.3 to 1.8) μg/mL and 1.8 (1.5 to 2.2) μg/mL, respectively. The median (range) lamivudine and zidovudine t_{max} values were 0.75 (0.50 to 2.00) hours and 0.50 (0.25 to 2.00) hours respectively. The extent (AUC) of lamivudine and zidovudine absorption and estimates of half-life following administration of *COMBIVIR* with food were similar when compared to fasting subjects, although the rate of absorption ($C_{max,}$ t_{max}) was slowed. Based on these data *COMBIVIR* 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 characteristics of the active ingredient and the *in vitro* dissolution behaviour of lamivudine-zidovudine tablets in water, 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 (less than 36% serum albumin *in vitro*). Zidovudine plasma protein binding is 34% to 38%. Interactions with medicinal products involving binding site displacement are not anticipated with *COMBIVIR*.

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 concentrations 2 to 4 hours 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 (5 to 10%) and low plasma binding.

The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50 to 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 (greater than 70%) via the organic cationic transport system.

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.

Special Patient Populations

- **Elderly**

The pharmacokinetics of lamivudine and zidovudine have not been studied in patients over 65 years of age.

- **Children**

In children over the age of 5 to 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 to 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 hr μM or 10.7 hr μg/mL) as doses of 200 mg six times daily in adults (40.7 hr μM or 10.9 hr 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.

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55 to 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 (from three months to 12 years; approximately 6 kg to 40 kg) is 8 mg/kg/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 2 to less than 6 years of age may be reduced by about 30% compared with other age groups. Further data to support this conclusion are currently awaited. At present, the available data do not suggest that lamivudine is less efficacious in this age group.

- **Renal Impairment**

Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction, due to decreased renal clearance. Dose reduction is required for patients with creatinine clearance of less than 30 mL/min. Zidovudine concentrations have also been shown to be increased in patients with advanced renal failure.

- **Hepatic Impairment**

Limited data in patients with cirrhosis suggest that 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.

- **Pregnancy**

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

Clinical Studies

The Antiretroviral Pregnancy Registry (APR) has received reports of over 11,000 exposures to lamivudine during pregnancy resulting in live birth. These consist of over

4,500 exposures during the first trimester, over 7,200 exposures during the second/third trimester and included 143 and 207 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.1% (2.6, 3.7%) and in the second/third trimester, 2.9% (2.5, 3.3%). The APR has received reports of over 13,000 exposures to zidovudine during pregnancy resulting in live birth. These consist of over 4,100 exposures during the first trimester, over 9,300 exposures during the second/third trimester and included 133 and 264 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.2% (2.7, 3.8%) and in the second/third trimester, 2.8% (2.5, 3.2%). These proportions are not significantly higher than those reported in the two population based surveillance systems (2.72 per 100 live births and 4.17 per 100 live births respectively). The Antiretroviral Pregnancy Registry does not show an increased risk of major birth defects for lamivudine or zidovudine compared to the background rate.

Non-Clinical Information

No synergy of toxicity has been observed in studies with lamivudine in combination with zidovudine. The clinically relevant effects of the two medicinal products in combination are anaemia, neutropenia and leucopenia.

Carcinogenesis, mutagenesis

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. There were no other zidovudine-related tumours observed in either sex of either species. 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. The predictive value of rodent carcinogenicity studies for humans is uncertain and thus the clinical significance of these findings is unclear.

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.

It is concluded that the transplacental carcinogenicity data from the first study represents a hypothetical risk, whereas the reduction in risk of maternal transfection of HIV to the uninfected child by the use of zidovudine in pregnancy has been well proven.

Neither lamivudine nor zidovudine are mutagenic in bacterial tests, but like many nucleoside analogues they show activity in *in vitro* mammalian tests such as the mouse lymphoma assay. Lamivudine has not shown any genotoxic activity in *in vivo* studies at doses that gave plasma concentrations up to 40 to 50 times higher than clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

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. The clinical implications of these findings are unknown.

Reproductive toxicology

In reproductive studies in animals both lamivudine and zidovudine were shown to cross the placenta, this has also been confirmed in humans. 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.

Neither zidovudine nor lamivudine have shown evidence of impairment of fertility in studies in male and female rats.

PHARMACEUTICAL INFORMATION

List of Excipients

***Tablet core*:**
Microcrystalline cellulose, sodium starch glycollate, colloidal silicon dioxide, magnesium stearate.

***White tablet film coat*:**
Hydroxypropylmethyl cellulose, titanium dioxide, macrogol 400, polysorbate 80.

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Nature and Contents of Container

Opaque polyvinyl chloride film with aluminium foil blister pack or high density polyethylene (HDPE) bottle with a child-resistant closure.

Incompatibilities

Not applicable.

Use and Handling

There are no special requirements for use or handling of this product.

Not all presentations are available in every country.

GSK is committed to the effective collection and management of human safety information relating to our products and we encourage health care professionals to report adverse events to us via phone call to +254-20-6933200 or email us on ke.safety@gsk.com

Full prescribing information is available on request from GlaxoSmithKline, P.O Box 78392-00507 Nairobi, Kenya or via our Healthcare Professionals Website www.gskpro.com

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