

DATA SHEET

Combivir[®] Tablets

Lamivudine 150mg & Zidovudine 300mg tablets

Presentation

COMBIVIR film-coated tablets contain 150mg lamivudine and 300mg zidovudine.

Combivir film-coated tablets are white to off-white capsule-shaped engraved with GXFC3 on one side.

Do not halve tablet.

Uses

Actions

Pharmacotherapeutic group - nucleoside analogue.

Lamivudine and zidovudine are potent, selective inhibitors of HIV-1 and HIV-2. Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Both active substances are 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 monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine and zidovudine triphosphates show significantly less affinity for host cell DNA polymerases.

In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*. Lamivudine therefore has, *in vitro*, a high therapeutic index.

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 <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 AZT 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 antiretrovirally-naïve patients as well as in patients presenting with viruses containing the M184V mutations.

Pharmacokinetics

Absorption: Lamivudine and zidovudine are well absorbed from the gut. The bioavailability of oral lamivudine in adults is normally between 80-85% and for zidovudine 60-70%. A bioequivalence study compared COMBIVIR with 3TC 150mg and Retrovir 300mg tablets taken together. The effect of food on the rate and extent of absorption was also studied. COMBIVIR was shown to be bioequivalent to 3TC 150mg and Retrovir 300mg given as separate tablets, when administered to fasting subjects.

Following COMBIVIR administration, lamivudine and zidovudine C_{max} (95% confidence interval) values were 1.5 (1.3-1.8)mg/mL and 1.8 (1.5-2.2)mg/mL 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 (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.

Distribution: Intravenous studies with lamivudine and zidovudine showed that the mean apparent volume of distribution is 1.3 and 1.6L/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 2-4 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 (5-10%) and low plasma binding.

The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50-80% of the administered dose eliminated by renal excretion. 3'-amino-3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

Elimination: The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32L/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 1.6L/h/kg. Renal clearance of zidovudine is estimated to be 0.34L/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys.

Renally impaired: 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 50mL/min. Zidovudine concentrations have also been shown to be increased in patients with advanced renal failure.

Hepatically impaired: 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.

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

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.

Indications

COMBIVIR is indicated for the treatment of HIV infected adults and adolescents over the age of 12 years, with progressive immunodeficiency ($CD_4 = \text{Count} = < 500 \text{ cells/mm}^3$).

Dosage and Administration

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

The recommended dose of COMBIVIR is one tablet twice daily. COMBIVIR may be administered with or without food. Do not halve the tablet.

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 (3TC™) and zidovudine (Retrovir™) are available in tablets/capsules and oral solution.

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

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

Dosage adjustments in patients with haematological adverse reactions:- Dosage adjustment of zidovudine may be necessary if the haemoglobin level falls below 9g/dL or 5.59mmol/L or the neutrophil count falls below $1.0 \times 10^9/L$ (see Contraindications and Warnings and Precautions). As dosage adjustment of COMBIVIR is not possible separate preparations of zidovudine and lamivudine should be used.

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.

Contraindications

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

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

Warnings and Precautions

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

Patients should be advised that current antiretroviral therapy, including COMBIVIR, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Patients treated with 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 (1200-1500mg/day), in patients with advanced HIV disease and in those who had poor marrow reserve prior to treatment (see Adverse Effects). 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 9g/dL (5.59mmol/L) or neutrophil count less than $1.0 \times 10^9/L$. As dosage adjustment of COMBIVIR is not possible separate preparations of zidovudine and lamivudine should be used (see Contraindications).

Children: COMBIVIR is not indicated for children under 12 years of age as appropriate dose reduction for the weight of the child cannot be made.

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 to any patient, and 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 or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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

Whilst all members of the PI and NRTI classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicate that there are differences in the risk between individual members of the respective therapeutic classes.

In addition, the lipodystrophy syndrome has a multi-factorial aetiology; with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles.

The long-term consequences of these events are currently unknown.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed 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 jirovecii* (*P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

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 is particularly important in patients with a known history of zidovudine induced anaemia.

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.

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.

Trimethoprim:- Administration of trimethoprim/sulphamethoxazole 160mg/800mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no 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* (*P. carinii*) pneumonia and toxoplasmosis has not been studied.

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

Interactions relevant to zidovudine:

Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated metabolite. 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 PCP 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.

Ribavirin:- The nucleoside analogue ribavirin antagonises the *in vitro* antiviral activity of zidovudine and so concomitant use of COMBIVIR with this medicinal product should be avoided.

Rifampicin:- Limited data suggests that co-administration of zidovudine and rifampicin decreases AUC of zidovudine by $48\% \pm 34\%$. 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

Pregnancy:

The safety of lamivudine in human pregnancy has not been established. 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. However, no such data are available for lamivudine. Both lamivudine and zidovudine have been shown to cross the placenta. Although animal reproductive studies (see Preclinical Safety Data) are not always predictive of the human response, administration of COMBIVIR during the first three months of pregnancy is not recommended unless the benefit to the mother outweighs the risk to the foetus.

Based on the animal carcinogenicity and mutagenicity findings for zidovudine (see Preclinical Safety Data) a carcinogenic risk to humans cannot be excluded. The relevance of these findings to both infected and uninfected infants exposed to zidovudine is unknown. However, 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 under any circumstances in order to avoid transmission of HIV. Both lamivudine and zidovudine are excreted in human milk at similar concentrations to those found in serum. Since lamivudine, zidovudine and HIV virus pass into breast milk it is recommended that mothers taking COMBIVIR do not breast feed their infants.

Fertility:

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

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 Effects

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 Special Warnings and Special Precautions for use).

Redistribution/accumulation of body fat (see Warnings and Precautions). The incidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.

Nervous system disorders

Common: Headache

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

Gastrointestinal disorders

Common: Nausea, vomiting, upper abdominal pain, diarrhoea

Rare: Pancreatitis, although a causal relationship to treatment is uncertain.
Rises in serum amylase.

Hepatobiliary disorders

Uncommon: Transient rises in liver enzymes (AST, ALT)

Skin and subcutaneous tissue disorders

Common: Rash, alopecia

Musculoskeletal and connective tissue disorders

Common: Arthralgia, muscle disorders

Rare: Rhabdomyolysis

General disorders and administration site conditions

Common: Fatigue, malaise, fever

Zidovudine:

Blood and lymphatic system disorders

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

These occur more frequently at higher dosages (1200-1500mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD₄⁺ cell counts less than 100/mm³. 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 B₁₂ 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

Rare: Lactic acidosis (see Special Warnings and Special Precautions for use), anorexia.

Redistribution/accumulation of body fat (see Warnings and Precautions). The incidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.

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

Overdosage

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. No fatalities occurred, and all patients recovered.

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

Pharmaceutical Precautions

Incompatibilities

None reported.

Shelf-life

2 years.

Special precautions for storage

Store below 30°C.

Instructions for use/handling

None required.

Medicines Classification

Prescription Only Medicine

Package Quantities

Tamper-evident cartons containing opaque polyvinyl chloride/foil blister packs. Each pack contains 60 coated tablets.

Further Information

Preclinical Safety Data

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.

Mutagenicity:- 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 40-50 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 is unknown.

Carcinogenicity:- 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 (420mg/kg/term body weight).

In a second study, mice were administered zidovudine at doses up to 40mg/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.

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.

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

List of Excipients

Tablet core: Microcrystalline cellulose, Sodium starch glycollate, Colloidal silicon dioxide, Magnesium stearate.

Tablet film coat: Hydroxypropylmethyl cellulose, Titanium dioxide, Macrogol 400, Polysorbate 80.

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.

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