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.

PHARMACEUTICAL FORM
Film-coated tablets.

Access to Medicines Markets Only:
For markets where Access to Medicines packs are registered:
COMBIVIR tablets contain 150 mg lamivudine and 300 mg zidovudine and are red capsule-shaped, scored tablets, engraved with A22 on both faces.

CLINICAL PARTICULARS
Indications
COMBIVIR is indicated for the treatment of HIV infection.

Dosage and Administration
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.

• 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 50 ml/min (see Pharmacokinetics). It is therefore recommended that separate preparations of lamivudine and zidovudine should be administered to these patients.

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

• Dosage adjustments in patients with haematological adverse reactions
Dosage adjustment of zidovudine may be necessary if the haemoglobin level falls below 9 g/dl or 5.59 mmol/l or the neutrophil count falls below 1.0 x 109/l (see Contraindications and Warnings and Precautions). As dosage adjustment of COMBIVIR is not possible separate preparations of zidovudine and lamivudine should be used.
Contraindications
The use of COMBIVIR is contra-indicated 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 x 10⁹/l), or abnormally low haemoglobin levels (less than 7.5 g/dl or 4.65 mmol/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 (1200-1500 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 x 10⁹/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 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 Reactions). 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 multifactorial 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 jiroveci (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 160 mg/800 mg (cotrimoxazole) 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.

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 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.

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 COMBIVIR.

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 Pre-clinical 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 peripartum 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 peripartum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lactation: Health experts recommend that where possible HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV.

Both 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.

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 in 10
- **common:** ≥1 in 100 and <1 in 10
- **uncommon:** ≥1 in 1,000 and <1 in 100
- **rare:** ≥1 in 10,000 and <1 in 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). 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 (1200-1500 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/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**

Common: Hyperlactataemia.

Rare: Lactic acidosis (see Warnings and Precautions), 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.
Overdose
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 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
Pharmacotherapeutic group - nucleoside analogue, ATC Code: J05 AF30.

Mechanism of Action
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.
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 <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 endpoint data indicate that lamivudine in combination with zidovudine alone or in combination with zidovudine containing treatment regimens results in a significant reduction in the risk of disease progression and mortality.

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

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 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 Cmax (95% confidence interval) values were 1.5 (1.3-1.8) µg/ml and 1.8 (1.5-2.2) µg/ml, respectively. The median (range) lamivudine and zidovudine tmax 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 (Cmax, tmax) 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 1.6 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.

Elimination
The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (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 5-6 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%. Cmax levels were 4.45 μM (1.19 μg/ml) following a dose of 120 mg zidovudine (in solution)/m² body surface area and 7.7 μM (2.06 μg/ml) at 180 mg/m² body surface area. Dosages of 180 mg/m² 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/m² zidovudine three times daily and again after switching to 180 mg/m² twice daily. Systemic exposures (daily AUC and Cmax) 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 55-65%) 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-12 ranging from approximately 3,800 to 5,300 h/ml. Recent findings indicate that exposure in children 2 to <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 50 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.

**Pre-clinical 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.

**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
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 PARTICULARS
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.

Red tablet film coat:
- Opadry red: Hydroxypropylmethyl cellulose, titanium dioxide, polyethylene glycol, allura red, sunset yellow

Incompatibilities
Not applicable.

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
Do not store above 30oC.

Nature and Contents of Container
Tamper-evident cartons containing opaque polyvinyl chloride/foil blister packs or white high density polyethylene (HDPE) bottle with a child-resistant closure. Each pack type contains 60 tablets.
Not all presentations are available in every country.
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