AUSTRALIAN PRODUCT INFORMATION

COMBIVIR (lamivudine and zidovudine) film-coated tablets

1 NAME OF THE MEDICINE

Lamivudine and zidovudine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

COMBIVIR Tablets are a fixed combination product containing lamivudine 150 mg and zidovudine 300 mg in each tablet. Product information for 3TC (tablets and oral solution) and RETROVIR (capsules and syrup) contain additional information specific for lamivudine and zidovudine, respectively.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

COMBIVIR tablets are available as both scored and unscored tablets.

COMBIVIR unscored tablets are white to off-white capsule-shaped film-coated tablets, engraved with “GXFC3” on one tablet face.

COMBIVIR scored tablets are white to off-white capsule-shaped film-coated tablets, engraved with “GXFC3” on both tablet faces.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

COMBIVIR is indicated for use alone or in combination with other antiretroviral therapies in the treatment of HIV infection.

4.2 DOSE AND METHOD OF ADMINISTRATION

COMBIVIR may be administered with or without food. Food reduces the C_{max} and extends the T_{max} of lamivudine but the amount of drug absorbed is not reduced. The clinical significance of this is not known (see Section 5.2 PHARMACOKINETIC PROPERTIES).

For situations where discontinuation of therapy with one of the active constituents of COMBIVIR, or dose reduction is necessary, separate preparations of lamivudine (3TC tablets and oral solution) and zidovudine (RETROVIR Capsules and Syrup) are available.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. For patients who are unable to swallow tablets, the tablet(s) may be crushed and 100% of the crushed tablet could be added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see Section 5.2 PHARMACOKINETIC PROPERTIES).

The dosing regimens for paediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling and supported by data from clinical studies using the individual components lamivudine and zidovudine. A pharmacokinetic overexposure of zidovudine can occur; therefore close safety monitoring is warranted in these patients.

COMBIVIR tablets should not be used for children weighing less than 14 kg, since doses cannot be appropriately adjusted for the weight of the child. For these patients and for patients, who are unable to swallow tablets, oral solutions of lamivudine and zidovudine are available.

For children <3 months of age, sufficient data are not available to make specific dosing recommendations. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adults and adolescents weighing at least 30 kg
The recommended dose of COMBIVIR is one tablet twice daily, giving a total daily dose of 600 mg zidovudine and 300 mg lamivudine.

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 and zidovudine should be taken as separate formulations according to the prescribed dosing for these products.

Monitoring of patients
Haematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of haematologic indices is recommended to detect serious anaemia or granulocytopenia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In patients who experience haematologic toxicity, reduction in haemoglobin may occur as early as 2 to 4 weeks, and granulocytopenia usually occurs after 6 to 8 weeks.

Dose adjustment
Significant anaemia (haemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant granulocytopenia (granulocyte count of <750 cells/mm^3 or reduction of >50% from baseline) require a dose interruption until evidence of marrow recovery is observed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). For less severe anaemia or granulocytopenia, a reduction in daily dose may be adequate. In patients who develop significant anaemia, dose modification does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose modification, gradual increases in dose may be appropriate depending on haematologic indices and patient tolerance. As dosage adjustment of COMBIVIR is not possible, separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the complete prescribing information for these drugs.

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 alterations in haematological parameters.

Dosage adjustment in renal insufficiency
Lamivudine and zidovudine concentrations are increased in patients with renal impairment due to decreased clearance. Therefore, as dosage adjustment of these may be necessary, it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance ≤50 mL/min) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Compared to healthy subjects, patients with advanced renal failure have a 50% higher maximum plasma concentration of zidovudine. Systemic exposure (measured as area under the zidovudine concentration time curve) is increased 100%; the half-life is not significantly altered. In renal failure there is substantial accumulation of the major glucuronide metabolite compared to healthy volunteers but this does not appear to cause toxicity (see Table 1).

Table 1

Mean Pharmacokinetic Parameters				
	Zidovudine		GAZT	
	Control (n=6)	Uraemic (n=19)	Control (n=6)	Uraemic (n=19)
C_{max} (μmol/L)	4.0 ± 0.4	6.2 ± 0.6*	14.9 ± 1.4	31.6 ± 0.9***
AUC (μmol.hr/L)	5.2 ± 0.6	11.7 ± 1.1**	23.7 ± 1.9	402.9 ± 88.6**
$t_{1/2}$ (hr)	1.0 ± 0.2	1.4 ± 0.1	0.9 ± 0.1	8.0 ± 2.0*

Data are mean values ± SE
*p < 0.05, ** p< 0.01, ***p< 0.001

Haemodialysis and peritoneal dialysis have no significant effect on zidovudine elimination. In a small number of patients haemodialysis would appear to be more efficient in eliminating the glucuronide metabolite than peritoneal dialysis. Intermittent dialysis is unlikely to require further dose modification from that defined by creatinine clearance.

Dosage adjustment in hepatic insufficiency
Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Dosage adjustments may be necessary but precise recommendations cannot be made at present. If monitoring of plasma zidovudine levels is not feasible, physicians will need to pay particular attention to signs of intolerance and increase the interval between doses as appropriate. It is recommended that separate preparations of zidovudine and lamivudine be administered to patients with severe hepatic impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.3 CONTRAINDICATIONS

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

As zidovudine is contraindicated in patients with abnormally low neutrophil counts (<0.75 x 10^9/L), or abnormally low haemoglobin levels (<7.5 g/dL or 4.65 mmol/L), COMBIVIR is contraindicated in these patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients receiving COMBIVIR or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV infection.

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 employed.

The full safety and efficacy profiles of the active ingredients in COMBIVIR have not been completely defined, particularly in regard to prolonged use.

Haematological effects
Therapy with zidovudine preparations is commonly associated with haematologic toxicity including granulocytopenia and severe anaemia requiring transfusions, particularly in patients with advanced HIV disease (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuance of the drug.

Because anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients with advanced symptomatic HIV disease receiving zidovudine, haematological parameters should be carefully monitored in patients receiving COMBIVIR (see Section 4.3 CONTRAINDICATIONS). These haematological effects are not usually observed before four to six weeks of 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. Decreases in the haemoglobin level of more than 25% from baseline and falls in the neutrophil count of more than 50% from baseline may require more frequent monitoring.

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 e.g. haemoglobin <9 g/dL or granulocyte count <1000 cells/mm^3 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). As dosage adjustment of COMBIVIR is not possible, separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the individual product information for these drugs.

Hypersensitivity
Sensitisation reactions, including anaphylaxis in one patient, have been reported in individuals receiving zidovudine therapy. Patients experiencing a rash should undergo medical evaluation.

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

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 zidovudine 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 life style 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.

Lactic acidosis and 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).

Immune reconstitution syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral 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. 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 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.

Special precautions for use
It is recommended that separate preparations of lamivudine and zidovudine should be administered in cases where dosage adjustment is necessary (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Physicians should refer to the individual product information for these drugs.

Use of paracetamol and other medicines
Zidovudine recipients who used paracetamol during the controlled trial in advanced HIV disease had an increased incidence of granulocytopenia which appeared to be correlated with the duration of paracetamol use.

If COMBIVIR is co-administered with other drugs metabolised by glucuronidation, careful thought should be given to the possibilities of interactions with zidovudine, because the toxicity of either drug may be potentiated (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Patients should be cautioned about the concomitant use of self-administered medications (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Osteonecrosis
Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Use in hepatic impairment
COMBIVIR should be used with caution in patients with HIV and chronic hepatitis B virus infection as 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 lamivudine is discontinued in a patient with HIV and HBV coinfection, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

The use of COMBIVIR in patients with hepatic impairment is discussed under Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Use in renal impairment
In patients with moderate to severe renal impairment, the terminal plasma half-life of lamivudine exposure is increased due to decreased clearance. Dosage adjustment in these patients is better controlled using individual zidovudine and lamivudine preparations as the dose frequency of lamivudine may need to be reduced (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use
The dosing guidelines for the use of COMBIVIR fixed dose tablet in children in the bodyweight range 14-30 kg are based on 360-480 mg/m^2/day for zidovudine and 8 mg/kg/day for lamivudine given as 2 or 3 divided doses in the clinical trials involving children. The extrapolation to weight based regime results in only approximate rather than accurate dosing. More accurate dosing can be achieved with use of separate oral solutions of Zidovudine and Lamivudine.

For children weighing less than 14 kg, COMBIVIR fixed dose tablet is not recommended for use, as long as correct dosing with it is not possible. Oral solutions must be used in these children.

For children <3 months of age, sufficient data are not available to make specific dosing recommendations. (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Effects on laboratory tests
See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Table 3.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interaction with other medicines
As COMBIVIR contains lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur with COMBIVIR. The likelihood of interactions with lamivudine is low due to limited metabolism and plasma protein binding and almost complete renal clearance. Similarly, zidovudine has limited protein binding but is eliminated primarily by hepatic conjugation to an inactive glucuronidated metabolite.

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.

As experience of drug interactions with COMBIVIR is limited, care should be taken when combining with other drug regimens. The interactions listed below should not be considered exhaustive but are representative of the classes of drug where caution should be exercised.

Interactions relevant to lamivudine
The possibility of interaction with other drugs administered concurrently with COMBIVIR should be considered, particularly when the main route of elimination is active renal secretion especially via the cationic system e.g. trimethoprim.

Sorbitol
Co-administration 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% (9 – 20%), 32% (28 – 37%), and 36% (32 – 41%) in lamivudine exposure (AUC_{∞}) and 28% (20 – 34%), 52% (47 – 57%), and 55% (50 – 59%) in the C_{max} of lamivudine in adults. When possible, avoid chronic co-administration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic co- administration cannot be avoided.

Trimethoprim
Administration of trimethoprim, as trimethoprim/sulfamethoxazole 160 mg/800 mg, causes an increase in lamivudine plasma levels. However, unless the patient already has renal impairment, no dosage adjustment of lamivudine is necessary. The effects of higher doses of trimethoprim on lamivudine plasma levels have not been investigated. Lamivudine has no effect on the pharmacokinetics of trimethoprim/sulfamethoxazole. Administration of lamivudine in patients with renal impairment should be assessed carefully.

Other medicines
In *in vitro* studies, ciprofloxacin, pentamidine and ganciclovir reduced the anti-HIV activity of lamivudine. The clinical significance of this is not known.

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.

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. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.

Interactions relevant to zidovudine
Changes in zidovudine plasma levels when co-administered with lamivudine were not statistically significant. Zidovudine has no effect on the pharmacokinetics of lamivudine (see Section 5.2 PHARMACOKINETIC PROPERTIES).

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.

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.

Paracetamol
Paracetamol use during treatment with zidovudine in a placebo-controlled trial was associated with an increased incidence of neutropenia especially following chronic therapy. However, the available pharmacokinetic data indicate that paracetamol does not increase plasma levels of zidovudine nor of its glucuronide metabolite.

Phenytoin
Phenytoin blood levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. These observations suggest that phenytoin levels should be carefully monitored in patients receiving COMBIVIR and phenytoin since many patients with advanced HIV infections have CNS conditions which may predispose to seizure activity.

Rifampicin
Limited data suggests that co-administration of zidovudine and rifampicin decreases AUC of zidovudine.

Other medicines
Co-administration of zidovudine with drugs that are nephrotoxic, cytotoxic, or which interfere with RBC/WBC number or function (e.g. pyrimethamine, sulfamethoxazole and trimethoprim, doxorubicin, dapsone, systemic pentamidine, ganciclovir, amphotericin B, flucytosine, vincristine, vinblastine, adriamycin or interferon) may increase the risk of adverse reactions

to zidovudine. If concomitant therapy with COMBIVIR and any of these drugs is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced.

Probenecid may reduce renal excretion of zidovudine and in addition, like some other drugs (e.g. codeine, methadone, morphine, inosine pranobex, paracetamol, aspirin, or indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone) may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).Careful thought should be given to the possibilities of drug interactions before using such drugs, particularly for chronic therapy, in combination with COMBIVIR.

Some experimental nucleoside analogues affecting DNA replication antagonise the *in vitro* antiviral activity of zidovudine against HIV and thus, concomitant use of such drugs should be avoided.

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

Some drugs such as trimethoprim and sulfamethoxazole, aerosolised pentamidine, pyrimethamine, and aciclovir may be necessary for the management or prevention of opportunistic infections. In the controlled trial in patients with advanced HIV disease, increased toxicity was not detected with limited exposure to these drugs. However, there is one published report of neurotoxicity (profound lethargy) associated with concomitant use of zidovudine and aciclovir (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – Interactions relevant to lamivudine).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Neither orally administered zidovudine (225 mg/kg BID) nor lamivudine (up to 70 times anticipated clinical exposure based on C_{max}) have shown evidence of impairment of fertility in male and female rats. There are no data on their affect on human female fertility. In men zidovudine has not been shown to affect sperm count, morphology or motility.

Use in pregnancy
(Pregnancy Category B3)

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 Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

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 lamivudine and zidovudine 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 Section 5.2 PHARMACOKINETIC PROPERTIES). 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. Pregnant women considering using lamivudine-zidovudine during pregnancy should be made aware of these findings.

There are limited data regarding the use of zidovudine in human pregnancy. It is not known whether zidovudine can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity.

In reproductive studies in animals, oral doses of both lamivudine and zidovudine were shown to cross the placenta. Lamivudine caused an increase in early embryonic deaths in the rabbit at exposures (based on C_{max} and AUC) less than the maximum anticipated clinical exposure. Oral zidovudine caused an increase in foetal resorptions in the rat (75 mg/kg BID) and rabbit (250 mg/kg BID). Lamivudine was not teratogenic in rats and rabbits with exposure (based on C_{max}) up to 40 and 36 times respectively those observed in humans at the clinical dosage. At maternally toxic doses, zidovudine (3000 mg/kg/day) given to rats during organogenesis resulted in an increased incidence of malformations. No evidence of foetal abnormalities were observed at lower doses.

Vaginal tumours have been seen in rodents following 19-month daily oral dosing with zidovudine at exposures (based on AUC) more than 4 times (mouse) and more than 27 times (rat) the estimated clinical exposure (see Section 5.3 PRECLINICAL SAFETY DATA). The relevance of these findings to either infected or 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.

Use in lactation

Health experts recommend that where possible HIV infected women do not breastfeed 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 breastfeeding during antiretroviral therapy.

Following oral administration of lamivudine or zidovudine to lactating rats, the respective drug was excreted in the milk. 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 microgram/mL) at similar concentrations to those found in maternal 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 breast milk:maternal plasma 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 nanogram/mL and were not detectable in one of the studies (assay sensitivity 7 nanogram /mL). Zidovudine median infant serum concentration was 24 nanogram/mL in one study and was below assay limit of qualification (30 nanogram/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 compound measured is unknown.

4.7 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 drug. Nevertheless, the clinical status of the patient and the adverse event profile of both lamivudine and zidovudine should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Information regarding the safety of COMBIVIR, zidovudine or lamivudine in combination with other antiretroviral drugs is limited. Physicians should refer to the complete product information for the respective antiretroviral therapy for a description of the known associated adverse reactions.

As COMBIVIR contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of added toxicity following concurrent administration of the two compounds.

Adverse reactions with COMBIVIR

Clinical-trial data
In a clinical study in twenty-four healthy volunteers the following adverse reactions possibly or probably related to COMBIVIR (or lamivudine 150 mg with Zidovudine 300 mg taken separately) were recorded - headache (4 subjects), nausea (4), disturbances of vision (1), phlebitis (1).

Post-marketing data
There is little experience with COMBIVIR currently.

Adverse reactions to combinations of lamivudine and zidovudine

Clinical-trial data

Table 2 lists all adverse events, occurring at an incidence of 5% or more, reported in controlled pivotal clinical trials in adults, irrespective of the investigator's assessment of the possible relationship to the study drug.

Table 2: Common adverse events (frequency ≥ 5.0%) reported in four pivotal, controlled clinical trials in adults.

	ZDV	ZDV + LAM (150)	ZDV + LAM(300)	ZDV + DDC(0.75)
n=	230	251	318	86
BLOOD AND LYMPHATIC				
Lymphatic signs & symptoms	4.8	9.2	7.2	11.6
Decreased white cells	3.5	5.2	5.0	9.3
EAR NOSE AND THROAT				
Throat & tonsil discomfort & pain	9.6	9.2	11.6	14.0
Viral ear nose & throat infection	7.4	9.6	6.9	12.8
Ear nose & throat infection	7.0	10.8	11.3	12.8
Sinusitis	6.5	6.8	7.2	4.7
Upper respiratory inflammation	1.7	5.2	3.8	3.5
GASTROINTESTINAL				
Abdominal discomfort & pain	9.1	8.4	11.3	8.1
Fungal gastrointestinal infection	5.2	6.4	7.5	14.0
Gastrointestinal discomfort & pain	5.2	7.2	4.1	5.8
Gaseous symptoms	2.6	5.2	3.1	2.3
LOWER RESPIRATORY				
Bronchitis	4.8	10.0	4.7	5.8
Breathing disorders	3.5	5.6	4.1	3.5
MUSCULOSKELETAL				
Musculoskeletal pain	9.6	12.0	13.5	22.1
Muscle pain	5.7	8.4	3.5	11.6
NEUROLOGY				
Headache	27.0	35.1	28.9	33.7
Neuropathy	10.0	12.4	8.5	23.3
Sleep disorders	7.0	10.8	11.6	8.1
Dizziness	3.9	10.4	6.0	9.3
NON-SITE SPECIFIC				
Viral infection	4.3	7.6	6.6	20.9
SKIN				
Sweating	7.0	7.6	6.3	7.0
Fungal skin infection	6.1	5.6	4.1	7.0
Acne & folliculitis	3.9	6.8	3.5	11.6
Viral skin infection	3.5	5.2	4.7	7.0

Common laboratory abnormalities observed during therapy are listed in Table 3.

Table 3: Frequencies of common laboratory abnormalities in 4 pivotal, controlled clinical trials in adults*

Test (Abnormal Level)	lamivudine 150 mg b.i.d. plus zidovudine 600 mg/day % (n)	zidovudine % (n)
Neutropenia (ANC<750/mm^3)	7.2% (237)	5.4% (222)
Anaemia (Hb<8.0 g/dL)	2.9% (241)	1.8% (218)
Thrombocytopenia (platelets<50,000/mm^3)	0.4% (240)	1.3% (223)
ALT (>5.0 x ULN)	3.7% (241)	3.6% (224)
AST (>5.0 x ULN)	1.7% (241)	1.8% (223)
Bilirubin (>2.5 ULN)	0.8% (241)	0.4% (220)
Amylase (>2.0 ULN)	4.2% (72)	1.5% (133)

ULN = Upper limit of normal ANC = absolute neutrophil count
n = Number of patients assessed
* Frequencies of these laboratory abnormalities were higher in patients with mild laboratory abnormalities at baseline.

Lamivudine appears to be well tolerated and most serious adverse events reported in clinical trials are not considered to be drug related. Adverse reactions from the 4 pivotal studies in adult patients receiving the recommended dose of lamivudine (150 mg bd) in combination with zidovudine 600 mg/day are included in Table 4 together with serious adverse reactions reported in large scale open studies.

Table 4: Adverse drug reactions reported in controlled trials and open studies.

Adverse reactions reported in controlled clinical trials - (n= 251) Lamivudine 150mg bd + zidovudine 600mg/day	**Serious adverse reactions reported in open studies (n= 17,572), Lamivudine 300mg bd (n=10,575), Lamivudine 150mg bd (n=6997), generally in combination with other antiretroviral therapy**
Non-site specific *Very common* Malaise and fatigue *Common* Fever	**Non-site specific** *Rare* Malaise and fatigue, fever
Blood and Lymphatic *Common* Anaemia, Decreased white cells	**Blood and Lymphatic** *Uncommon* Decreased white cells *Rare* Anaemia Thrombocytopenia
Neurological *Very common* Headache *Common* Neuropathy	**Neurological** *Rare* Neuropathy Headaches Paraesthesia
Gastrointestinal *Very Common*	**Gastrointestinal** *Rare*

Nausea *Common* Diarrhoea Discomfort and pain Vomiting	Nausea and vomiting Abdominal discomfort and pain Diarrhoea
Hepatobiliary tract and pancreas *Common* Abnormal liver function tests *Uncommon* Pancreatitis	**Hepatobiliary tract and pancreas** *Uncommon* Pancreatitis *Rare* Abnormal pancreatic enzymes Abnormal liver function tests
Skin *Common* rashes	**Skin** *Very rare* rashes

Cases of pancreatitis have occurred rarely in adult patients and more commonly in children. Treatment with lamivudine should be stopped immediately if clinical signs or symptoms or laboratory abnormalities suggestive of pancreatitis occur.

In paediatric patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis, the combination of lamivudine with other antiretroviral therapies should be used with extreme caution and only if there is no satisfactory alternative therapy.

Post-marketing data
The following events have been reported during therapy for HIV disease with lamivudine alone and in combination with other antiretroviral agents.

Musculoskeletal: arthralgia, muscle disorders including rarely rhabdomyolysis.

Skin: alopecia (rare).

Haematological: pure red cell aplasia (lamivudine and zidovudine); aplastic anaemia (zidovudine).

Metabolism and nutrition disorders
Hyperlactataemia (common)

Lactic acidosis (rare) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adverse reactions with zidovudine monotherapy
The frequency and severity of adverse events associated with the use of zidovudine are greater in patients with more advanced infection at the time of initiation of therapy. Tables 5, 6 and 7 summarise the relative incidence of haematologic adverse events observed in the placebo-controlled clinical studies by severity of HIV disease present at the start of treatment.

Table 5

Asymptomatic HIV Infection Study (n=1338)	Granulocytopenia (<750/mm^3)	Anaemia (Hb<8 g/dL)

	Zidovudine		Placebo	Zidovudine		Placebo
	1500 mg*	500 mg		1500 mg*	500 mg	
CD4 ≤500	6.4% (n=457)	1.8% (n=453)	1.6% (n=428)	6.4% (n=457)	1.1% (n=453)	0.2% (n=428)

Table 6

Early Symptomatic HIV Disease Study (n=713)	Granulocytopenia (<750/mm^3)		Anaemia (Hb<8 g/dL)	
	Zidovudine 1200 mg	Placebo	Zidovudine 1200 mg	Placebo
CD4 > 200	4% (n=361)	1% (n=352)	4% (n=361)	0% (n=352)

Table 7

Advanced Symptomatic HIV Disease Study (n=281)	Granulocytopenia (<750/mm^3)		Anaemia (Hb<7.5 g/dL)	
	Zidovudine 1500 mg*	Placebo	Zidovudine 1500 mg*	Placebo
CD4 > 200 CD4 < 200	10% (n=30) 47% (n=114)	3% (n=30) 10% (n=107)	3% (n=30) 29% (n=114)	0% (n=30) 5% (n=107)

*Three times the currently recommended dose in asymptomatic patients.

The most serious adverse reactions include 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), particularly in patients with CD4 cell counts less than 100/mm^3. Dosage reduction or cessation of therapy may become necessary (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).The anaemia appeared to be the result of impaired erythrocyte maturation as evidenced by increasing macrocytosis (MCV) while on drug.

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, and in those patients taking paracetamol concurrently (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Some of the HIV-infected individuals participating in these clinical trials had baseline symptoms and signs of HIV disease and/or experienced adverse events at some time during the study. It was often difficult to distinguish adverse events possibly associated with zidovudine administration from underlying signs of HIV disease or intercurrent illnesses. The possibility of such events being drug related, however, cannot be excluded. The following table summarises clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with zidovudine in the original placebo-controlled study. Of the items listed in Table 8, only severe headache, nausea, insomnia and myalgia were reported at a significantly greater rate in zidovudine recipients.

Table 8

Percentage (%) of Patients with Clinical Events in the Advanced HIV Disease Study					
Adverse Event	Zidovudine (n=144) %	Placebo (n=137) %	Adverse Event	Zidovudine (n=144) %	Placebo (n=137) %
BODY AS A WHOLE			MUSCULOSKELETAL		
Asthenia	19	18	Myalgia	8	2
Diaphoresis	5	4	NERVOUS		
Fever	16	12	Dizziness	6	4
Headache	42	37	Insomnia	5	1
Malaise	8	7	Paraesthesia	6	3
			Somnolence	8	9
GASTROINTESTINAL			RESPIRATORY		
Anorexia	11	8	Dyspnoea	5	3
Diarrhoea	12	18	SKIN		
Dyspepsia	5	4	Rash	17	15
GI Pain	20	19	SPECIAL SENSES		
Nausea	46	18	Taste Perversion	5	8
Vomiting	6	3			

Clinical adverse events which occurred in less than 5% of all patients treated with zidovudine in the advanced HIV study are listed below. Since many of these adverse events were seen in placebo-treated patients as well as zidovudine recipients, their possible relationship to the drug is unknown.

Body as a whole: body odour, chills, oedema of the lip, flu syndrome, hyperalgesia, back pain, lymphadenopathy, chest pain.
Cardiovascular: vasodilation.
Gastrointestinal: constipation, dysphagia, oedema of the tongue, eructation, flatulence, bleeding gums, rectal haemorrhage, mouth ulcer.
Hepatic: changes in liver function tests including increases in AST levels.
Musculoskeletal: arthralgia, muscle spasm, tremor, twitch, myopathy.
Nervous: anxiety, confusion, depression, emotional lability, nervousness, syncope, loss of mental acuity, vertigo, seizures.
Respiratory: cough, epistaxis, pharyngitis, rhinitis, sinusitis, hoarseness.
Skin: acne, pruritus, urticaria, nail pigmentation.
Special senses: amblyopia, hearing loss, photophobia.
Urogenital: dysuria, polyuria, urinary frequency, urinary hesitancy.
Metabolism and nutrition disorders: Treatment with zidovudine has been associated with loss of subcutaneous fat (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Subsequent to the initial trial, sensitisation reactions, including anaphylaxis in one patient, have been reported in individuals receiving zidovudine therapy.

All unexpected events and expected events of a severe or life-threatening nature were monitored in the placebo-controlled studies in early HIV disease and asymptomatic HIV infection. Data concerning the occurrence of additional signs or symptoms were also collected. No distinction was made in reporting events between those possibly associated with the administration of the study medication and those due to the underlying disease. Tables 9 and 10 summarise all those events reported at a statistically significant greater incidence for zidovudine recipients in these studies:

Table 9

Percentage (%) of Patients with Clinical Events in the Early Symptomatic HIV Disease Study		
Adverse Event	Zidovudine (n=361) %	Placebo (n=352) %
BODY AS A WHOLE		
Asthenia	69	62
GASTROINTESTINAL		
Dyspepsia	6	1
Nausea	61	41
Vomiting	25	13

Table 10

Percentage (%) of Patients with Clinical Events* in an Asymptomatic HIV Infection Study			
Adverse Event	1500 mg Zidovudine*** (n=457) %	500 mg Zidovudine (n=453) %	Placebo (n=428) %
BODY AS A WHOLE			
Asthenia	10.1	8.6**	5.8
Headache	58.0**	62.5	52.6
Malaise	55.6	53.2	44.9
GASTROINTESTINAL			
Anorexia	19.3	20.1	10.5
Constipation	8.1	6.4**	3.5
Nausea	57.3	51.4	29.9
Vomiting	16.4	17.2	9.8
NERVOUS			
Dizziness	20.8	17.9**	15.2

*Reported in ≥5% of study population
**Not statistically significant versus placebo
***Three times the currently recommended dose in asymptomatic patients.

The following events have also been reported in patients treated with zidovudine. The relationship between these events and the use of zidovudine is difficult to evaluate, particularly in the medically complicated situations which characterise advanced HIV disease. If the severity of the symptoms warrants it, a reduction or suspension of zidovudine therapy may assist in the assessment and management of these conditions:

- cardiomyopathy
- pancytopenia with marrow hypoplasia and isolated thrombocytopenia;
- lactic acidosis in the absence of hypoxaemia;
- liver disorders such as severe hepatomegaly with steatosis, raised blood levels of liver enzymes and bilirubin;
- pancreatitis;
- skin and oral mucosa pigmentation;
- hyperlactataemia;
- gynaecomastia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no experience of overdosage with COMBIVIR. However, there is limited data available on the consequences of ingestion of acute overdoses of either lamivudine or zidovudine in humans. No fatalities occurred, and all patients recovered. No specific signs or symptoms have been identified following such overdosage.

Treatment
Patients should be observed closely for evidence of toxicity (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) and given the necessary supportive therapy.

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 negligible effect on the removal of zidovudine. The primary metabolite, 3-azido-3-deoxy-5-O-β-Dglucopyranuronosylthymidine (GAZT), appears to be more efficiently removed by haemodialysis than peritoneal dialysis. For more details, physicians should refer to the individual product information for these preparations.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Zidovudine is an inhibitor of the *in vitro* replication of some retroviruses including HIV, whereas lamivudine is a potent, selective inhibitor of HIV-1 and HIV-2 replication *in vitro.* Both drugs are metabolised sequentially by intracellular kinases to their 5'-triphosphate (TP) derivatives. Lamivudine 5'-triphosphate and triphosphate are substrates for and competitive inhibitors of HIV reverse transcriptase. However, their main antiviral activity is through incorporation of the monophosphate form (MP) 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).

The relationships between *in vitro* susceptibility of HIV to lamivudine and zidovudine and the clinical response to therapy remain under investigation. *In vitro* sensitivity testing has not been standardised and results may vary according to methodological factors.

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. However *in vitro* studies also indicate that zidovudine-resistant virus isolates may become sensitive again to zidovudine when they simultaneously acquire resistance to lamivudine. Furthermore *in vivo* there is clinical evidence that lamivudine plus zidovudine delays the emergence of zidovudine resistance in antiretroviral naïve patients.

Clinical trials

Pregnancy
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.

Clinical endpoint study
Clinical endpoint data from a prospective study 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.

NUCB3007 (CAESAR) was a 20andomized20, double-blind, placebo-controlled study comparing continued current therapy [zidovudine (AZT) alone (62% of patients) or zidovudine with didanosine (ddI) or zalcitabine (ddC) (38% of patients)] to the addition of lamivudine or lamivudine plus an investigational non-nucleoside reverse transcriptase inhibitor, randomised 1:2:1. A total of 1,840 HIV-infected adults with 25 to 250 (median, 126) CD4 cells/mm^3 at baseline were enrolled: median age was 36 years, 87% were male, 83% were nucleoside-experienced, and 17% were therapy-naïve. The median duration of treatment for each group was current therapy* 327 days, lamivudine plus current therapy* 360 days and lamivudine plus NNRTI** plus current therapy* 360 days. Results are summarised in Table 11.

Table 11: Number of Patients (%) With At Least One HIV Disease Progression Event or Death

Endpoint	Current Therapy* (n = 471)	lamivudine plus Current Therapy* (n = 907)	lamivudine plus a NNRTI** plus Current Therapy* (n = 462)
HIV progression or death	95 (20%)	86 (9%)[†]	42 (9%)
Death	28 (6%)	23 (3%)[‡]	14 (3%)

*Current treatment = AZT (200 mg tds or 250 mg bd) monotherapy, AZT + ddI (250 mg bd) or AZT + ddC (0.75 mg tds).

**An investigational non-nucleoside reverse transcriptase inhibitor not approved in the Australia.

† p<0.0001 for lamivudine + current therapy vs current therapy alone.

‡ p= 0.0007 for lamivudine + current therapy vs current therapy alone.

The data showed there was a significant reduction in progression to the combined endpoint of a new AIDS event or death for patients who received lamivudine in combination with zidovudine containing regimens compared to patients maintained on zidovudine containing regimens alone (p<0.0001). The Hazard Ratio (HR) was 0.427 (95% confidence interval 0.318 – 0.572), or a 57% reduction in risk. In addition, the data indicated a significant reduction in death, regardless of causality, in the combination lamivudine plus zidovudine containing regimens as compared to the zidovudine containing regimens alone (p=0.0007); HR = 0.399 (95% CI 0.230-0.693) or a 60% reduction in risk.

ACTG320 was a randomised, double-blind, placebo-controlled study to compare indinavir, zidovudine (or stavudine) and lamivudine with the 2 drug regimen of zidovudine (or stavudine) and lamivudine in HIV-infected patients with CD4 counts ≤ 200 cells/mm^3. Patients had received ≥ 3 months prior zidovudine therapy and had no prior exposure to protease inhibitors. A total of 1156 patients were randomised. The median duration of follow-up was 38 weeks. During the study there were 96 new AIDS-defining events or deaths, 63 (11%) in the zidovudine/lamivudine arm and 33 (6%) in the zidovudine/lamivudine/indinavir arm (estimated Hazard Ratio 0.50). There were 13 (6%) deaths in the zidovudine/lamivudine arm and 5 (2%) in the zidovudine/lamivudine/indinavir arm (Hazard Ratio 0.37). Both these results were statistically significant.

Surrogate endpoint studies in adults

The approved indication for COMBIVIR is based on analyses of several surrogate endpoints in clinical studies of the combination of lamivudine 150 mg twice daily and zidovudine 200 mg three times daily. The subjects of these studies were patients with or without prior antiretroviral therapy.

Study designs are summarised in Table 12. All were randomised, double-blind, multicentre studies. The characteristics of the patients at baseline are given in Table 13.

There are no results of clinical studies of the combination of lamivudine 150 mg with zidovudine 300 mg taken twice daily. The approval of the use of zidovudine 300 mg twice daily in COMBIVIR is based on extrapolation from clinical studies in which several other dosage regimens have been used.

Table 12: Summary of pivotal efficacy studies in adults

					Summary of results			
					0-24 weeks		**0-52 weeks**	
Study design – Pivotal studies in adults					**Mean time-weighted change**		**52 week change from baseline**	
Report No (Protocol)	Study Design Patients	Treatment doses	Number random-ised	Duration of treatment	CD4	Log_{10} HIV RNA	CD4	Log_{10} HIV RNA
UCR/95/002	DB, MC	Lam 300mg bd	87	24 weeks DB	24	-0.59	-11	-0.32

(NUCA3001)	Zdv-naïve CD4 200-500	Zdv 200mg tds	93	DB continuation	17	-0.31	-53	-0.14
		Zdv + Lam 150mg	92		55	-1.12	61	-0.80
		Zdv + Lam 300mg	94		45	-1.15	60	-1.04
UCR/95/003 (NUCA3002)	DB, MC Zdv-experienced CD4 100-300	Zdv + ddC 0.75mg	86	24 weeks DB DB continuation	-2	-0.66	16	-0.50
		Zdv + Lam 150mg	84		38	-0.80	35	-0.48
		Zdv + Lam 300mg	84		39	-0.91	27	-0.55
GIO/94/003 (NUCB3001)	DB, MC Zdv-naïve CD4 100-400	Zdv 200mg tds	64	24 weeks DB OL continuation	18	-0.57		
		Zdv + Lam 300mg	65		75	-1.33		
GIO/94/005 (NUCB3002)	DB, MC Zdv-experienced CD4 100-400	Zdv 200mg tds	73	24 weeks DB OL continuation	-18	-0.07		
		Zdv + Lam 150mg	75		38	-0.96		
		Zdv + Lam 300mg	75		32	-0.77		

Zidovudine given at a dose of 200 mg tds in all studies. Lamivudine dosed bd in all studies.

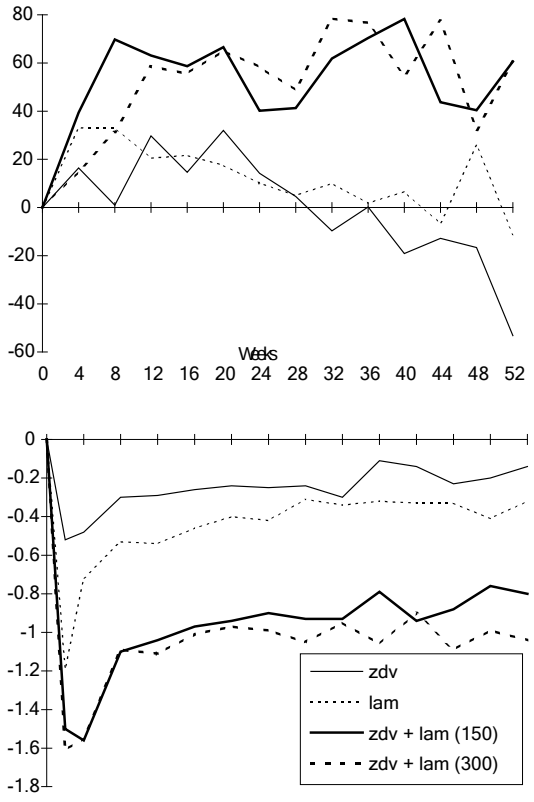
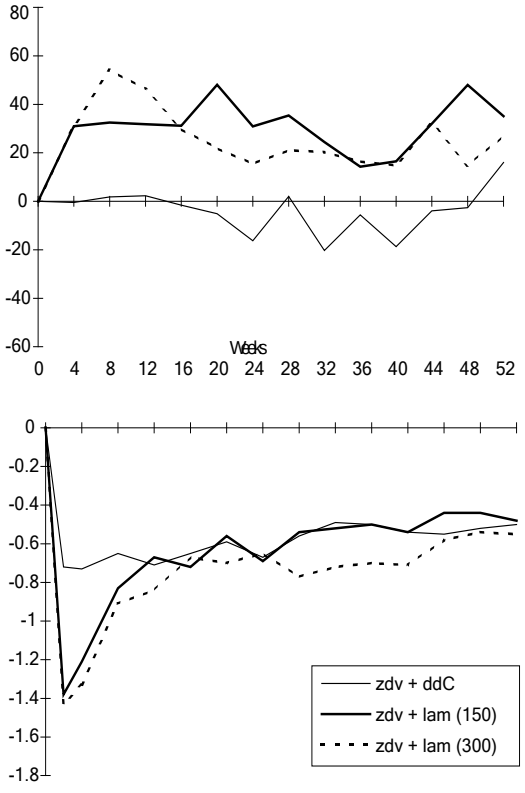
Table 13: Characteristics of patients 22andomized to pivotal studies.

	NUCA3001	NUCA3002	NUCB3001	NUCB3002
Number of patients	366	254	129	223
Age (median) years	34	37	33	36
Asymptomatic HIV infection	80%	58%	64%	53%
Duration of prior antiretroviral therapy (months)	<1	24	<1	23
baseline CD4 cells/mm^3 (median)	200 to 500 (352)	100 to 300 (211)	100 to 400 (260)	100 to 400 (241)

After 24 weeks: In zidovudine-naïve patients the combination of lamivudine and zidovudine resulted in a highly significant ($p<0.001$) increase in absolute CD4 cell count and reduction in $\log_{10}$ HIV RNA relative to zidovudine monotherapy (600 mg/day) or lamivudine monotherapy (600 mg/day). Similarly, in zidovudine-experienced patients, the combination of lamivudine and zidovudine resulted in significantly greater improvements in CD4 cell count than either zidovudine monotherapy (600 mg/day) or a combination of zidovudine and zalcitabine (600 mg/day + 0.75 mg) and a significantly greater reduction in $\log_{10}$ HIV-RNA than zidovudine monotherapy. A meta-analysis of the 4 pivotal trials showed that lamivudine in combination with zidovudine slowed the progression of HIV disease compared to 'controls' (all other treatment arms).

In the North American studies (NUCA3001 and NUCA3002) patients were allowed to remain in the study with blinding intact until the last patient had completed the 24 week assessment. Analysis of the subset of patients receiving treatment for at least 52 weeks established that the benefits on CD4 cell count and viral load were maintained compared to zidovudine monotherapy over this period ($p<0.001$). Results for CD4 count and $\log_{10}$ HIV-RNA are given in figure 1.

Figure 1	Results from North American studies for effects on primary surrogate parameters in zidovudine-naïve and zidovudine experienced patients

Zidovudine-naïve patients: **NUCA3001**	Zidovudine-experienced patients: **NUCA3002**
Mean change in absolute CD4 from baseline	Mean change in absolute CD4 from baseline
	
Mean change in HIV-RNA from baseline	Mean change in HIV-RNA from baseline

5.2 PHARMACOKINETIC PROPERTIES

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 in healthy volunteers compared COMBIVIR and lamivudine (3TC) 150 mg tablets and zidovidine (Retrovir) 300 mg tablets taken together.

In fasted subjects, COMBIVIR was shown to be bioequivalent to lamivudine 150 mg and zidovudine 300 mg administered together as separate tablets. Following COMBIVIR administration, the C_{max} (95% confidence interval) for lamivudine was 1.5 microgram/mL (1.3-1.8) and for zidovudine was 1.8 microgram/mL (1.5-2.2). The median t_{max} (range) was 0.75 hours (0.50-2.00) and 0.50 hours (0.25-2.00) for lamivudine and zidovudine, 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 fasted subjects.

The rate of absorption, however, was reduced for both drugs. For lamivudine, mean C_{max} was 85% of that in the fasted state while median t_{max} increased from 0.75 to 1.5 hours. For zidovudine, the mean C_{max} was 55% of that in the fasted state while the median t_{max} was increased from 0.5 to 1.0 hours. The clinical significance of the effect of food on the absorption of COMBIVIR is not known.

Pharmacokinetics in special patient groups
There are limited data on the pharmacokinetics of zidovudine in patients with renal or hepatic impairment. Dosage adjustment of zidovudine is required in patients with advanced renal failure and severe hepatic impairment. There are also limited data on the pharmacokinetics of zidovudine in pregnant women. No specific data are available on the pharmacokinetics of zidovudine in the elderly.

A single dose pharmacokinetic study of lamivudine (n=16) in HIV-infected patients with normal renal function and with moderate (creatinine clearance <30 mL/min and >10 mL/min) or end stage renal impairment (creatinine clearance <10 mL/min) showed there was a linear relationship between lamivudine clearance and renal function.

Since dosage adjustments of lamivudine are required in patients with impaired renal function and for zidovudine in patients with advanced renal failure or severe hepatic impairment the use of a fixed dose combination tablet such as COMBIVIR is not recommended in these patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 ingredients 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
From intravenous studies, the mean volume of distribution of lamivudine is 1.3 L/kg. Plasma protein binding is limited. Zidovudine plasma protein binding is 34% to 38%.

Limited data shows relatively low penetration of lamivudine into the central nervous system. When individually administered the mean ratio cerebrospinal fluid/serum concentration for lamivudine and zidovudine 2 to 4 hours after dosing was approximately 0.12 and 0.5 respectively.

Metabolism
The likelihood of adverse drug interactions with lamivudine is low due to limited metabolism (<10% hepatic) and plasma protein binding and almost complete renal elimination. An interaction with trimethoprim, a constituent of trimethoprim with sulphamethoxazole, causes a 40% increase in lamivudine exposure following administration of one trimethoprim 160 mg/sulfamethoxazole 800 mg tablet once daily for 5 days. The effects of higher doses of trimethoprim on lamivudine plasma levels have not been investigated.

Zidovudine is rapidly metabolised during first pass to 3'-azido- 3'-deoxy- 5'-O-β-D-glucopyranuronosylthymidine (GAZT) which has an apparent elimination half-life of 1 hour (range 0.61 to 1.73 hours). Following oral administration, urinary recoveries of zidovudine and GAZT accounted for 14 and 74% of the dose, respectively, and the total urinary recovery averaged 90% (range 63 to 95%), indicating a high degree of absorption.

Limited data has identified 3'-amino- 3'deoxythymidine (AMT) as a metabolite of zidovudine following intravenous and oral dosing. A small *in vitro* study showed that AMT reduced the growth of haemopoietic progenitor cells; the clinical significance of this finding is unknown.

Excretion
Mean terminal half-life of elimination of lamivudine is 5 to 7 hours and mean systemic clearance is approximately 0.32 L/h/kg, with predominantly renal clearance (>70%) via active tubular secretion, but little (<10%) hepatic metabolism.

Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance ≤50 mL/min (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

The mean terminal half-life of elimination of zidovudine is approximately one hour. Renal clearance of zidovudine is estimated to be 0.34 L/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

Limited data indicate that zidovudine crosses the placenta and is found in amniotic fluid and foetal blood. Zidovudine has also been detected in semen. Lamivudine crosses the placenta in rats and rabbits.

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%. C_{ssmax} levels were 4.45 microM (1.19 microgram/ml) following a dose of 120 mg zidovudine (in solution)/m^2 body surface area and 7.7 microM (2.06 microgram/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 microM or 10.7 hr microgram/ml) as doses of 200 mg six times daily in adults (40.7 hr microM or 10.9 hr microgram/ml).

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

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age. Due to these differences, the recommended dose for lamivudine in children (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 5,800 nanogram.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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
With zidovudine no evidence of mutagenicity (with or without metabolic activation) was observed in the *Salmonella* mutagenicity assay. In a mutagenicity assay conducted in L5178Y/TK+/- mouse lymphoma cells, zidovudine was weakly mutagenic in the presence and absence of metabolic activation. In an *in vitro* cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities. Zidovudine was clastogenic in *in vivo* micronucleus tests in rats and mice. Zidovudine gave positive results in an *in vitro* mammalian cell transformation assay.

Lamivudine was not active in a microbial mutagenicity screen but did induce mutations at the thymidine kinase locus of mouse lymphoma L5178Y cells without metabolic activation. Lamivudine was clastogenic in human peripheral blood lymphocytes *in vitro*, with or without metabolic activation. In rats, lamivudine did not cause chromosomal damage in bone marrow cells *in vivo* or cause DNA damage in primary hepatocytes.

No mutagenicity studies have been carried out using a combination of lamivudine and zidovudine.

Carcinogenicity
Zidovudine was administered orally to separate groups of mice and rats at doses up to 40 and 300 mg/kg/day, respectively. In mice, seven late-appearing (after 19 months) vaginal neoplasms (5 non-metastasising squamous cell carcinomas, one squamous cell papilloma, and one squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle dose animal. No vaginal tumours were found at the lowest dose. In rats, two late-appearing (after 20 months), non-metastasising vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumours occurred at the low or middle dose in rats. No other drug related tumours were observed in either sex of either species. At doses that produced tumours in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 4 times (mouse) and 27 times (rat) the estimated human exposure at the recommended therapeutic dose of one tablet twice daily.

When lamivudine was administered orally to separate groups of rodents at doses up to 2000 times (mice and male rats) and 3000 (female rats) mg/kg/day, there was no evidence of a carcinogenic effect due to lamivudine in the mouse study. In the rat study there was an increased incidence of endometrial tumours at the highest dose (approximately 70 times the estimated human exposure at the recommended therapeutic dose of one tablet twice daily, based on AUC). However, the relationship of this increase to treatment is uncertain.

No carcinogenicity studies have been carried out using a combination of lamivudine and zidovudine.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain microcrystalline cellulose (460), sodium starch glycollate, silicon dioxide, magnesium stearate (572), hypromellose (464), titanium dioxide (171), macrogol 400 and polysorbate 80 (433).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablets are available in blister packs or plastic bottles. Each pack type contains 60 tablets.

Not all container types may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

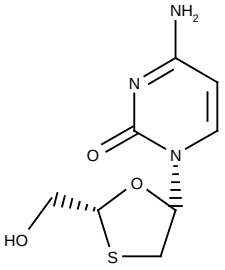
Lamivudine is a white to off-white crystalline solid which is highly soluble in water.

Zidovudine is a white to off-white, odourless, crystalline solid.

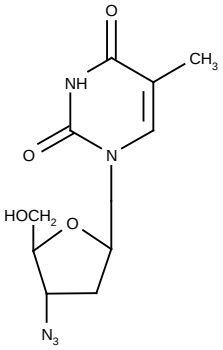
Lamivudine is the free base of (2R-cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one; with a molecular weight of 229.3 and molecular formula $C_8H_{11}N_3O_3S$.

The chemical name of zidovudine (formerly called azidothymidine (AZT)) is 3'-azido-3'-deoxythymidine; with a molecular weight of 267.24 and molecular formula $C_{10}H_{13}N_5O_4$.

Chemical structure
Lamivudine structural formula is shown below:



Zidovudine structural formula is shown below:



CAS number
134678-17-4 (lamivudine); 30516-87-1 (zidovudine).

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

ViiV Healthcare Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria, 3067
Australia

9 DATE OF FIRST APPROVAL

23 January 1998

10 DATE OF REVISION

12 February 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI Reformat
6.4	Addition of Storage Conditions

Version 10.0