AUSTRALIAN PRODUCT INFORMATION

RETROVIR (zidovudine)
capsules and syrup

1 NAME OF THE MEDICINE

Zidovudine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

RETROVIR Capsules 100 mg: Each capsule contains zidovudine 100 mg.

RETROVIR Capsules 250 mg: Each capsule contains zidovudine 250 mg.

RETROVIR Syrup: Each 5 mL contains zidovudine 50 mg, sodium benzoate, saccharin sodium, maltitol solution.

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

3 PHARMACEUTICAL FORM

RETROVIR Capsules 100 mg: Opaque white cap and body coded GSYJU.

RETROVIR Capsules 250 mg: Opaque blue cap and opaque white body coded GSJV2.

RETROVIR Syrup: Pale yellow, strawberry flavoured.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RETROVIR (zidovudine) is indicated for use in the treatment of HIV infection, alone and in combination with other antiretroviral therapies. The optimal dosage for this indication has not been established.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults weighing at least 30 kg
A broad range of dosage regimens has been employed; a daily dose of 500-600 mg in two to five divided doses has been used commonly world wide.

Dosage in combination therapy
RETROVIR may be administered separately or with other antiretroviral therapies (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials - Combination therapy).

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/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.

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 in renal impairment
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 (see Table 1 below) but this does not appear to cause toxicity.

Table 1: Mean Pharmacokinetic Parameters

	Zidovudine		GAZT (3'-azido- 3'-deoxy- 5'-O-β-D-glycopyranuronosylthymidine)	
	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

Patients with advanced renal failure should receive RETROVIR at the lower end of the dosage range. Haematological parameters and clinical response may influence the need for subsequent dosage adjustment. 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.

Dosage in 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 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.

Dosage adjustments in recipients of combination therapy
For recipients of combination antiretroviral therapy, dosage adjustments for the drugs should follow guidelines for the individual drug. For severe adverse events, those in which the causative drug is unclear, or those persisting after dose interruption or reduction of one drug, the other drug(s) should also be interrupted or dose-reduced. Physicians should refer to the complete product information for the respective antiretroviral drug for a description of the associated adverse reactions.

4.3 CONTRAINDICATIONS

RETROVIR preparations are contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulation.

RETROVIR should not be given to patients with abnormally low neutrophil counts (less than 0.75×10^9/L) or abnormally low haemoglobin levels (less than 7.5 g/dL or 4.65 mmol/L).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings
Therapy with RETROVIR (zidovudine) is commonly associated with haematologic toxicity including granulocytopenia and severe anaemia requiring transfusions particularly in patients with advanced HIV disease.

Precautions
Patients receiving zidovudine 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 associated diseases.

The full safety and efficacy profile of zidovudine has not been completely defined, particularly in regard to prolonged use.

Zidovudine should be used with extreme caution in patients who have bone marrow compromise evidenced by a granulocyte count < 1000/mm^3 or haemoglobin < 9.5 g/dL. In all of the placebo-controlled studies, but most frequently in patients with advanced symptomatic HIV disease, anaemia and granulocytopenia were the most significant adverse events observed (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.

Significant anaemia most commonly occurred after 4 to 6 weeks of therapy and in many cases required dose adjustment, discontinuation of zidovudine, and/or blood transfusions. Frequent (at least every 2 weeks) blood counts are strongly recommended in patients with advanced HIV disease taking zidovudine. For asymptomatic HIV-infected individuals and patients with early HIV disease, most of whom have better marrow reserve, blood counts

may be obtained less frequently, depending upon the patient's overall status. If anaemia or granulocytopenia develops, dosage adjustments may be necessary (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

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

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 (COMBIVIR 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 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 zidovudine, particularly to those with known risk factors for liver disease. Treatment with zidovudine 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 (IRIS)
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. 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.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV-negative children should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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.

Information for patients
In order to ensure the safe and effective use of zidovudine it is necessary that the patient should be made adequately aware of the benefits and risks associated with its use. It is recommended that the following information, in addition to any other considered appropriate by the treating clinician, should be provided to the patient. Zidovudine is not a cure for HIV infections, and patients may continue to acquire illnesses associated with HIV, including opportunistic infections. Therefore, patients should be advised to seek medical care for any significant change in their health status.

Patients should be informed that the drug has been extensively studied but for limited periods of time, and that long term safety and efficacy are not known, particularly for patients without symptoms or with less advanced disease. Patients should be informed that the major toxicities of zidovudine are granulocytopenia and/or anaemia.

The frequency and severity of these toxicities are greater in patients with more advanced disease and those who initiate therapy later in the course of their infection. They should be told that if toxicity develops, they may require transfusions or dose modifications including possible discontinuation. They should be told of the extreme importance of having their blood counts followed regularly while on therapy and especially closely for patients with

advanced symptomatic HIV disease. They should be cautioned about the use of other medications such as paracetamol that may exacerbate the toxicity of zidovudine (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

RETROVIR Capsules, Tablets and Syrup are for oral ingestion only. Patients should be told of the importance of taking zidovudine exactly as prescribed. They should be told not to share medication and not to exceed the recommended dose. Patients should be told that the long-term effects of zidovudine are unknown at this time.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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

Use in renal impairment
The use of zidovudine in patients with renal impairment is discussed under Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Zidovudine is eliminated from the body following metabolism (glucuronidation) primarily by renal excretion; only a small fraction is excreted unchanged in the urine.

Use in the elderly
The use of zidovudine in the elderly is discussed under Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use
Safety and effectiveness in children have not been established.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

As experience of drug interactions with zidovudine 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.

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

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 toxicity. If concomitant therapy with 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.

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 RETROVIR.

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 zidovudine.

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 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 zidovudine since many patients with advanced HIV infections have CNS conditions which may predispose to seizure activity.

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 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
No effect on male or female fertility (judged by conception rates) was seen in rats given zidovudine orally at doses up to 225 mg/kg twice daily.

There are no data on the effect of zidovudine on human female fertility. In men zidovudine has not been shown to affect sperm count, morphology or motility.

Use in pregnancy
(Category B3)

Zidovudine has been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 13,000 women during pregnancy and postpartum. Available human data from the APR do not show an increased risk of major birth defects for zidovudine compared to the background rate (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

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

Zidovudine crosses the human placenta. Zidovudine has been associated with findings in animal reproductive studies. Pregnant women considering using zidovudine during pregnancy should be made aware of these findings. It is fetotoxic in animals. Oral teratology studies in the rat and in the rabbit at doses up to 250 mg/kg twice daily revealed no evidence of teratogenicity with zidovudine. The incidence of foetal resorptions was increased in rats given 75 or 225 mg/kg twice daily and rabbits given 250 mg/kg twice daily: dosages which give plasma levels of > 19.5 and 200.7 μM respectively at 30 minutes after dosing. A separate study, reported subsequently, has shown that 3000 mg/kg/day (as two equal doses at least 6 hours apart) given to rats during the period of organogenesis, caused marked maternal toxicity and an increased incidence of foetal malformations. This dose is comparable to the single oral median lethal dose of 3683 mg/kg in the rat. No evidence of increased incidence of foetal abnormality was observed in this study at the lower dose rates administered - 600 mg/kg/day or less, also given as 2 equal doses.

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.

It is not known whether zidovudine can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. Zidovudine should be given to a pregnant woman only if clearly needed.

Use in lactation
Excretion of zidovudine in breast milk has been reported in clinical studies, resulting in sub-therapeutic infant plasma levels.

Breast feeding is not advised because of the potential for HIV transmission from mother to child, and the potential risk of adverse events due to antiretroviral drug excretion in breast milk.

In settings where formula feeding is unsafe or unavailable, the World Health Organisation has provided Guidelines.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of 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 zidovudine should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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. The following tables 2, 3 and 4 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 2: Incidence of haematologic adverse events observed in patients with asymptomatic HIV infection

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)

*Three times the currently recommended dose in asymptomatic patients.

Table 3: Incidence of haematologic adverse events observed in patients with early symptomatic HIV disease

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 4: Incidence of haematologic adverse events observed in patients with advanced symptomatic HIV disease

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 the 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 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. Table 5 below 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 the table, only severe headache, nausea, insomnia and myalgia were reported at a significantly greater rate in zidovudine recipients.

Table 5: 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	19	18	MUSCULO-SKELETAL	8	2
Asthenia	5	4	Myalgia		
Diaphoresis	16	12	NERVOUS	6	4
Fever	42	37	Dizziness	5	1
Headache	8	7	Insomnia	6	3
Malaise			Paraesthesia	8	9
			Somnolence		
GASTRO-INTESTINAL	11	8	RESPIRATORY	5	3
	12	18	Dyspnoea		
Anorexia	5	4	SKIN	17	15
Diarrhoea	20	19	Rash		
Dyspepsia	46	18	SPECIAL	5	8
GI Pain	6	3	SENSES		
Nausea			Taste		
Vomiting			Perversion		

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, generalised 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 SGOT 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.

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. The

following tables 6 and 7 summarise all those events reported at a statistically significant greater incidence for zidovudine recipients in these studies:

Table 6: 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 7: 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
GASTRO-INTESTINAL			
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. They may occur as part of the underlying disease process or as a result of the wide range of drugs used in the management of HIV disease. The relationship between these events and the use of zidovudine is therefore 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;

- red cell aplasia and aplastic anaemia

Adverse reactions with combination therapy
Information regarding the safety of zidovudine 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.

Only limited safety data are available on the combined use of zidovudine with zalcitabine. Clinical adverse events occurring in > 3% of patients treated with zalcitabine 0.005 and 0.01 mg/kg every eight hours administered concomitantly with zidovudine 100 mg or 200 mg every eight hours, as well as zidovudine 50 mg every eight hours alone or combined with zalcitabine 0.005 mg/kg every eight hours, are listed in Table 8 below. One patient with advanced HIV disease died of refractory acidosis, mild pancreatitis, hepatomegaly with steatosis, and an unexplained neurological syndrome. The investigator assessed this event as remotely related to zidovudine and/or the combination of zidovudine and zalcitabine.

Table 8: Percentage of Patients with Clinical Adverse Experiences Considered Possibly or Probably Related to Study Drug Occurring in > 3% of Patients

	Zidovudine + Zalcitabine Combination Trial Pooled Concomitant Regimens[a]	**N3447/ACTG106[b] No Prior ZDV n=47**
Body System/Adverse Event	**Mild/moderate/severe**	**Moderate/severe**
Peripheral Neuropathy	21%	4%
Gastrointestinal		
Nausea	36.2%	8.5%
Oral Ulcers	27.7%	4.3%
Abdominal Pain	21.3%	8.5%
Diarrhoea	14.9%	10.6%
Vomiting	14.9%	2.1%
Anorexia	12.8%	6.4%
Constipation	6.4%	2.1%
Dermatological		
Pruritus	14.9%	4.3%
Rash	14.9%	2.1%
Erythematous Rash	6.4%	2.1%
Night Sweats	6.4%	2.1%
Maculopapular Rash	4.3%	2.1%
Follicular Rash	4.3%	0.0%
Nervous System		
Headache	38.3%	8.5%
Musculoskeletal		
Myalgia	14.9%	2.1%
Arthralgia	8.5%	2.1%
Body as a Whole		
Fatigue	34.0%	8.5%
Fever	14.9%	2.1%
Rigours	8.5%	2.1%
Chest Pain	6.4%	2.1%

Weight Decrease	6.4%	4.3%
Respiratory Pharyngitis	8.5%	2.1%

a Excluded are 9 patients who received zidovudine alone for the greater part of the study. Only 8 patients were treated with the recommended combination regimen; all other patients were treated at lower doses of zalcitabine and/or zidovudine.

b Median duration of treatment ranged from 22 to 92 weeks among the arms.

Treatment with zidovudine has been associated with loss of subcutaneous fat (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Post marketing data

Metabolism and nutrition disorders

Hyperlactataemia (common)

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

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

No specific symptoms or signs have been identified following acute overdose with zidovudine, apart from those listed as undesirable effects.

Treatment

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

Haemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine. The primary metabolite, GAZT, appears to be more efficiently removed by haemodialysis than peritoneal dialysis.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

RETROVIR is the brand name for zidovudine (formerly called azidothymidine (AZT)), an antiretroviral drug active against human immunodeficiency virus (HIV).

Mechanism of action

Zidovudine is an inhibitor of the *in vitro* replication of some retroviruses including HIV (also known as HTLVIII, LAV or ARV). This drug is a thymidine analogue in which the 3'-hydroxy (-OH) group is replaced by an azido ($-N_3$) group. Cellular thymidine kinase converts zidovudine into zidovudine monophosphate. The monophosphate is further converted into the diphosphate by cellular thymidylate kinase and to the triphosphate derivative by other

cellular enzymes. Zidovudine triphosphate interferes with the HIV viral RNA dependent DNA polymerase (reverse transcriptase) and thus inhibits viral replication. Zidovudine triphosphate also inhibits cellular α-DNA polymerase, but at concentrations 100-fold higher than those required to inhibit reverse transcriptase. *In vitro,* zidovudine triphosphate has been shown to be incorporated into growing chains of DNA by viral reverse transcriptase. When incorporation by the viral enzyme occurs, the DNA chain is terminated. Studies in cell culture suggest that zidovudine incorporation by cellular α-DNA polymerase may occur, but only to a very small extent and not in all test systems. Chain termination has not been demonstrated with cellular α-DNA polymerase.

Microbiology

The relationship between *in vitro* susceptibility of HIV to zidovudine and the inhibition of HIV replication in man or clinical response to therapy has not been established. *In vitro* sensitivity results vary greatly depending upon the time between virus infection and zidovudine treatment, the particular assay used, the cell type employed, and the laboratory performing the test. In addition, the methods currently used to establish virologic responses in clinical trials may be relatively insensitive in detecting changes in the quantities of actively replicating HIV or reactivation of these viruses. Zidovudine blocked 90% of detectable HIV replication *in vitro* at concentrations of < 0.13 µg/mL (ID_{90}) when added shortly after laboratory infection of susceptible cells. This level of antiviral effect was observed in experiments measuring reverse transcriptase activity in H9 cells, PHA stimulated peripheral blood lymphocytes, and unstimulated peripheral blood lymphocytes. The concentration of drug required to produce a 50% decrease in supernatant reverse transcriptase was 0.013 µg/mL (ID_{50}) in both H9 cells and peripheral blood lymphocytes. Zidovudine at concentrations of 0.13 µg/mL also provided > 90% protection from a strain of HIV (HTLV IIIB) induced cytopathic effects in two tetanus-specific T4 cell lines. p24 gag protein expression was also undetectable at the same concentration in these cells. Partial inhibition of viral activity in cells with chronic HIV infection (presumed to carry integrated HIV DNA) required concentrations of zidovudine (8.8 µg/mL in one laboratory to 13.3 µg/mL in another) which are approximately 100 times as high as those necessary to block HIV replication in acutely infected cells. There are limited data on the development of resistance to zidovudine.

Reduced *in vitro* sensitivity to zidovudine has been reported for HIV isolates from patients who have received prolonged courses of zidovudine therapy. The available information indicates that for early HIV disease, the frequency and degree of reduction of *in vitro* sensitivity is notably less than for advanced disease.

The major metabolite of zidovudine, 3'-azido- 3'-deoxy- 5'-O-β-D-glycopyranuronosylthymidine (GAZT), does not inhibit HIV replication *in vitro.* GAZT does not antagonise the antiviral effect of zidovudine *in vitro* nor does GAZT compete with zidovudine triphosphate as an inhibitor of HIV reverse transcriptase.

The cytotoxicity of zidovudine for various cell lines was determined using a cell growth assay. ID_{50} values for several human cell lines showed little growth inhibition by zidovudine except at concentrations > 50 µg/mL. However, one human T-lymphocyte cell line was sensitive to the cytotoxic effect of zidovudine with an ID_{50} of 5 µg/mL. Moreover, in a colony-forming unit assay designed to assess the toxicity of zidovudine for human bone marrow, an ID_{50} value of < 1.25 µg/mL was estimated. Two of ten human lymphocyte cultures tested were found to be sensitive to zidovudine at 5 µg/mL or less.

Zidovudine has antiviral activity against some other mammalian retroviruses in addition to HIV. No significant inhibitory activity was exhibited against a variety of other human and animal viruses, except an ID_{50} of 1.4 to 2.7 µg/mL against the Epstein-Barr virus, the clinical significance of which is not known at this time.

No antagonistic effects *in vitro* were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine, lamivudine and interferon-alpha).

There is currently no evidence that zidovudine plus zalcitabine prevents the emergence of zidovudine-resistant isolates. However, *in vitro* studies with zidovudine-resistant virus isolates indicate such strains remain sensitive to zalcitabine.

Clinical trials

Monotherapy

Advanced HIV Disease

A randomized, double-blind, placebo-controlled trial (BW 02) of oral zidovudine (1500 mg/day) was conducted in 281 adults with advanced HIV disease which included 160 patients with AIDS and 121 patients with ARC.

There were 19 deaths (12 in patients with AIDS, 7 in patients with ARC) in the placebo group and 1 death (patient with AIDS) in the group receiving zidovudine. Treatment with zidovudine significantly improved the probability of survival for 24 weeks in both the AIDS and ARC subgroups. During a follow-up protocol with open-label treatment with zidovudine, patients who were initially randomized to receive zidovudine continued to have better overall survival than did patients initially randomized to placebo. Survival rates in the group of patients originally randomized to receive zidovudine declined to 85% after 1 year, 41% after 2 years, and 23% after 3 years. These survival rates may be lower than currently observed due to the absence of opportunistic infection prophylaxis in this study. Zidovudine also significantly reduced the risk of acquiring an AIDS-defining opportunistic infection, and patients who received zidovudine generally did better than the placebo group in terms of several other measures of efficacy including performance level, neuropsychiatric function, maintenance of body weight, and the number and severity of symptoms associated with HIV disease.

The weight of evidence indicates an overall beneficial effect of zidovudine on HIV-associated neurological disorders. However, the effectiveness of dosages less than 1000 mg/day in the treatment or prevention of HIV-associated neurological dysfunction is unknown.

Asymptomatic HIV Infection and Early HIV Disease (CD4 between 200 to 500 cells/mm^3)

The population indicated for monotherapy with zidovudine was extended to asymptomatic or symptomatic adults with CD4 cell counts of 500 cells/ mm^3 or less, based on the results of two randomized double-blind placebo-controlled trials (ACTG 019, ACTG 016) of 2051 adults. Treatment with zidovudine reduced the risk of progression to advanced HIV disease (ARC, AIDS or death) and significantly improved CD4 cell count. Survival benefit could not be assessed due to limited duration of follow-up at the time the placebo arms were discontinued. Other large studies of longer duration have not shown additional survival benefit of early versus delayed therapy with zidovudine above that seen for patients with advanced HIV disease.

Combination therapy

Combination therapy of zidovudine with zalcitabine or didanosine

A randomised, double-blind trial (ACTG 175) compared combinations of zidovudine (200 mg tds) plus didanosine (200 mg bd) or zalcitabine (0.75 mg tds) with zidovudine alone or didanosine alone. The trial was conducted in 2567 HIV-infected adults without AIDS and with CD4 cell counts ≥ 200 and ≤ 500 cells/mm^3 (mean 352 cells/mm^3), of whom 1067 were antiretroviral naive and 1400 had received more than 1 week of prior therapy (median > 18 months). Median duration of follow-up was 143 weeks.

Compared to zidovudine alone, zidovudine plus didanosine was associated with a significant reduction in combined study endpoint (decline in CD4 count, progression to an AIDS defining event or death) of 50% ($p < 0.001$) and the zidovudine plus zalcitabine combination was associated with a reduction of 46% ($p < 0.001$) in the combined study endpoint. In the overall trial (combined data for antiretroviral naive and antiretroviral experienced patients), statistically significant benefit of both of the two combinations was shown compared to zidovudine alone for the combined study endpoint.

Compared to zidovudine alone, zidovudine plus didanosine was associated with a significant reduction in combined clinical endpoint (progression to an AIDS defining event or death) of 35% ($p=0.025$) for antiretroviral experienced patients and 36% ($p=0.005$) for the overall trial. Compared to zidovudine monotherapy, zidovudine plus zalcitabine was associated with a significant reduction of 51% ($p=0.016$) in the combined clinical endpoint for antiretroviral naive patients.

Compared to zidovudine monotherapy, zidovudine plus didanosine showed a significant reduction in mortality of 48% ($p=0.019$) for antiretroviral experienced patients and of 45% ($p=0.008$) for the overall trial.

A randomised, double-blind trial (Delta) compared combination of zidovudine (200 mg tds) plus didanosine (200 mg bd) or zalcitabine (0.75 mg tds) with zidovudine alone. The trial was conducted in 3207 HIV-infected adults, with CD4 cell counts ≥ 50 and ≤ 350 cells/mm^3 (mean 205 cells/mm^3). 2124 participants were zidovudine naive (Delta 1) and 1083 participants had at least 3 months prior zidovudine (Delta 2). The median duration of follow-up was 30 months.

In the overall trial, in comparison to zidovudine alone, zidovudine plus didanosine was associated with a reduction in mortality of 33% ($p < 0.0001$) and zidovudine plus zalcitabine was associated with a reduction in mortality of 21% ($p=0.008$). In Delta 1, evidence of a survival benefit was strong in the combination treatment groups compared to zidovudine alone (overall $p < 0.0001$). In Delta 2, there was less evidence of a difference in mortality between combination treatment groups compared to zidovudine alone ($p=0.19$). Overall there was a delay in disease progression, with benefit seen mainly in participants who had not received zidovudine before.

Combination therapy of zidovudine with 3TC (lamivudine) or zalcitabine

Four double-blind, multicentre studies have been conducted in HIV-infected adults with (NUCA3001 and NUCB3001) or without (NUCA3002 and NUCB3002) prior antiretroviral therapy (Table 9). After 24 weeks, in zidovudine naive patients, the combination of zidovudine and lamivudine resulted in a significant increase in absolute CD4 count and

reduction on log_{10} HIV RNA relative to zidovudine monotherapy or lamivudine monotherapy. In zidovudine experienced patients, the combination of zidovudine and lamivudine resulted in significantly greater improvements in CD4 cell count than either zidovudine monotherapy or combination of zidovudine and zalcitabine and a significantly greater reduction in log_{10} HIV RNA than zidovudine monotherapy. In the zidovudine experienced groups, analysis of a subset of patients receiving treatment for at least 52 weeks established that the benefit of combined zidovudine and lamivudine treatment on CD4 cell count and viral load was maintained compared to zidovudine monotherapy.

Table 9: Summary of pivotal efficacy studies in adults

Study design				Summary of results			
				0-24 weeks		0-52 weeks	
				Mean time-weighted change		52 week change from baseline	
Study Design Patients	Treatment doses	Number random-ised	Duration of treatment	CD4	Log_{10} HIV RNA	CD4	Log_{10} HIV RNA
DB, MC zdv-naive	lam 300 mg bd	87	24 weeks DB	24	-0.59	-11	-0.32
	zdv 200 mg tds	93	DB continuation	17	-0.31	-53	-0.14
CD4 200-500	zdv + lam 150 mg	92		55	-1.12	61	-0.80
	zdv + lam 300 mg	94		45	-1.15	60	-1.04
DB, MC zdv-experienced CD4 100-300	zdv + ddC 0.75 mg	86	24 weeks DB	-2	-0.66	16	-0.50
	zdv + lam 150 mg	84	DB continuation	38	-0.80	35	-0.48
	zdv + lam 300 mg	84		39	-0.91	27	-0.55
DB, MC zdv-naive CD4 100-400	zdv 200 mg tds	64	24 weeks DB	18	-0.57		
	zdv + lam 300 mg	65	OL continuation	75	-1.33		
DB, MC zdv-experienced CD4 100-400	zdv 200 mg tds	73	24 weeks DB	-18	-0.07		
	zdv + lam 150 mg	75	OL continuation	38	-0.96		
	zdv + lam 300 mg	75		32	-0.77		

Zidovudine given at a dose of 200 mg tds in all studies. Lamivudine dosed bd in all studies. DB: double-blind study; OL: open-label study; MC: multicentre study; zdv: zidovudine; lam: lamivudine and ddC: zalcitabine.

Clinical end-point 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 multicenter, 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 3TC or 3TC 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-naive. The median duration of treatment for each group was current therapy* 327 days, 3TC plus current therapy* 360 days and 3TC plus NNRTI** plus current therapy* 360 days. Results are summarised in Table 10.

Table 10: Number of Patients (%) With At Least One HIV Disease Progression Event or Death – Intention to Treat Population

Endpoint	Current Therapy* (n = 471)	3TC plus Current Therapy* (n = 907)	3TC 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 3TC + current therapy vs current therapy alone.
‡ $p = 0.0007$ for 3TC + 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 is 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 randomized. 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.

Pregnancy
The Antiretroviral Pregnancy Registry (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%). This

proportion is 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 APR does not show an increased risk of major birth defects zidovudine compared to the background rate.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
After oral dosing, zidovudine was rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 0.5 to 1.5 hours. Kinetics appeared to be dose-independent over the range of 2 mg/kg every 8 hours to 10 mg/kg every 4 hours. The mean zidovudine half-life was approximately 1 hour and ranged from 0.78 to 1.93 hours following oral dosing. When zidovudine capsules are taken with food there is an increase in the time to achieve maximum plasma concentration and a reduction in maximum plasma concentration. There is a small and variable effect on overall exposure to zidovudine, as estimated by AUC. The clinical significance of these changes is not known. The effect of food on absorption of zidovudine syrup is not known.

Steady-state serum concentrations of zidovudine following chronic oral administration of 250 mg every 4 hours (3.0 to 5.4 mg/kg) were determined in 21 patients (body weight ranged from 46.0 to 83.6 kg) in a Phase II trial. Mean steady-state predose and 1.5 hours postdose zidovudine concentrations were 0.16 µg/mL (range 0 to 0.84 µg/mL) and 0.62 µg/mL (range 0.05 to 1.46 µg/mL), respectively.

Distribution
In adults, the average cerebrospinal fluid/plasma zidovudine concentration ratio 2-4 hours after dosing was found to be approximately 0.5. Limited data indicate that zidovudine crosses the placenta and is found in amniotic fluid and foetal blood. Zidovudine has also been detected in semen.

Metabolism
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). This reduces the bioavailability from the capsule formulation. Based on limited data the average oral capsule bioavailability appears to be 65% (range 52-75%). 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.

In a multiple dose bioavailability study conducted in 12 HIV-infected adults receiving doses of 100 mg or 200 mg every four hours, two formulations of zidovudine oral solution, one of which differed only slightly from the marketed formulation, were demonstrated to be bioequivalent to zidovudine capsules with respect to area under the concentration-time curve (AUC). The rate of absorption of zidovudine solution was greater than that of zidovudine capsules, as indicated by mean times to peak concentration of 0.5 and 0.8 hours,

respectively. Mean values for steady-state peak concentration (dose-normalised to 200 mg) were 1.5 and 1.2 mg/mL for solution and capsules, respectively.

Excretion
Renal clearance is estimated to be 400 mL/min/70 kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine plasma protein binding is 34 to 38%. The zidovudine cerebrospinal fluid (CSF) concentration measured 1.8 hours following oral dosing at 2 mg/kg was 0.04 µg/mL (n=1).

There are limited data on the pharmacokinetics of zidovudine in patients with renal or hepatic impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No evidence of mutagenicity (with or without metabolic activation) was observed in the Ames *Salmonella* mutagenicity assay. In a mutagenicity assay conducted in L5178Y/TK+/- mouse lymphoma cells, zidovudine was weakly mutagenic in the absence of metabolic activation only at the highest concentrations tested (4000 and 5000 µg/mL).

In the presence of metabolic activation, the drug was weakly mutagenic at concentrations of 1000 µg/mL and higher. In an *in vitro* cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities at concentrations of 3 µg/mL and higher. No such effects were noted at the two lowest concentrations tested, 0.3 and 1 µg/mL.

Zidovudine was clastogenic in an *in vivo* micronucleus test after multiple oral doses > 100 mg/kg/day in mice and 500 mg/kg/day in rats. Zidovudine was not clastogenic in rats after single IV dosages of 37.5 to 300 mg/kg.

A study of the peripheral blood lymphocytes of eleven AIDS patients showed a higher chromosome breakage frequency in those who had received zidovudine than in those who had not. The clinical significance of these findings is unclear.

Carcinogenicity
Zidovudine was administered orally at three dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60 and 120 mg/kg/day in mice and 80, 220 and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30 and 40 mg/kg/day after day 90 because of treatment-related anaemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, seven late-appearing (after 19 months) vaginal neoplasms (5 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) 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.

It is not known how predictive the results of rodent carcinogenicity studies may be for man. At the highest doses tested at which no tumours were reported the estimated drug exposure (as measured by AUC values) was more than 2 times (mouse) and more than 20 times (rat) the estimated human exposure at the recommended therapeutic dose of 500 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

RETROVIR Capsules 100 mg: Each capsule contains starch-maize, cellulose microcrystalline, sodium starch glycollate, magnesium stearate, gelatin, titanium dioxide and TekPrint SW-9008 Black ink or Opacode S-1-277002 Black.

RETROVIR Capsules 250 mg: Each capsule contains starch-maize, cellulose microcrystalline, sodium starch glycollate, magnesium stearate, gelatin, titanium dioxide, indigo carmine and TekPrint SW-9008 Black ink or Opacode S-1-277002 Black.

RETROVIR Syrup: Each 5 mL contains glycerol, citric acid, sodium benzoate, saccharin sodium, maltitol solution, Flavour Strawberry PHL-134189, Flavour White Sugar DA13780, and water-purified.

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. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

RETROVIR Capsules 100 mg: Bottles or blister packs of 100.

RETROVIR Capsules 250 mg: Blister packs of 40 or 60.

RETROVIR Syrup: Bottles of 200 mL with tamper-evident caps. Syringe, syringe adaptor and plastic cap supplied for use opening.

Not all strengths, dose forms, pack sizes, container types may be distributed in Australia.

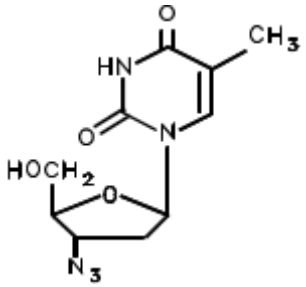
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. Zidovudine has a molecular weight of 267.24 and the molecular formula $C_{10}H_{13}N_5O_4$.

Chemical structure



CAS number
30516-87-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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

9 DATE OF FIRST APPROVAL

02 August 1991

10 DATE OF REVISION

02 November 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Update to the statement on the risk of transmission of infection
4.9	Removal of specific ADRs in the overdose section, rewording and addition of cross-reference to section 4.8

Version 10.0