APPROVED PACKAGE INSERT
RETROVIR ORALS

QUALITATIVE AND QUANTITATIVE COMPOSITION:

RETROVIR S Syrup: Oral syrup containing 50 mg zidovudine per 5 ml.

The active substance is zidovudine.

Contains sweeteners:

Maltitol solution 3.2 g per 5mL

Saccharin sodium 10.0mg per 5mL

Glycerol 500 mg per 5mL

Preservative: Sodium benzoate 0.2% *m/v*

The other ingredients are:

Citric acid, strawberry flavour, artificial candied sugar flavour, purified water.

CLINICAL INFORMATION

INDICATIONS:

RETROVIR Oral Formulations are indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and children.

Evidence of efficacy has been demonstrated in adult patients with T4 (T-helper) cell counts of less than 500/mm^3 whether or not associated with symptoms.

Efficacy has also been demonstrated for the management of patients with advanced HIV disease, such as those with Acquired Immune Deficiency Syndrome (AIDS) or AIDS-related complex (ARC). Results from open-labelled studies in children with symptomatic HIV infection and markers indicative of significant immune suppression are consistent with experience in adults.

RETROVIR is indicated in pregnancy to reduce the rate of maternal-foetal transmission of HIV. However, infants of these mothers should not be breast fed.

The following table provides details of the antiretroviral studies which have been carried out for the reduction of maternal-foetal transmission of HIV:

Antiretroviral interventions to reduce MTCT of HIV of proven efficacy:

Study	Drug (Patient no.)	Treatment				Transmission rate: Active vs placebo [Relative efficacy]
		Mother			Infant	
		Antepartum	Intrapartum	Postpartum		
No breast-feeding						
PACTG 076	Zidovudine (n = 239)	100mg 5x/day, (po) (from week	At onset: 2mg/kg (iv) for 1 hr, then	No	2mg/kg 6 hourly (po)	At 18 months: 8.3% vs 25.5%

		14 – 34)	1mg/kg/hr		(for 6 weeks)	[Efficacy: 68%]
Thai	Zidovudine (n = 198)	300mg 2x/day (po) (from week 36)	At onset: 300mg, then 3 hourly (po)	No	No	At 6 months: 9.4% vs 18.9% [Efficacy: 50%]
Harvard University Thai						
Arm LL	Zidovudine (n = 419)	300mg 2x/day (po) (from week 28)	300mg 3 hourly	No	2mg/kg qid (for 6 weeks)	Kaplan Meier: 6.5%
Arm LS	Zidovudine (n = 350)	300mg 2x/day (po) (from week 28)	300mg 3 hourly	No	2mg/kg qid (for 3 days)	4.7%
Arm SL	Zidovudine (n = 345)	300mg 2x/day (po) (from week 35)	300mg 3 hourly	No	2mg/kg qid (for 6 weeks)	8.6%
Arm SS	Zidovudine (n = 236)	300mg 2x/day (po) (from week 35)	300mg 3 hourly	No	2mg/kg qid (for 3 days)	10.5%
Breast-feeding						
Ivory Coast	Zidovudine (n = 139)	300mg 2x/day (po) (from week 36)	At onset: 300mg, then 3 hourly (po)	No	No	At 3 months: 15.7% vs 24.9% [Efficacy: 37%]
Ivory Coast/ Burkina Faso	Zidovudine (n = 209)	300mg 2x/day (po) (from week 36 – 38)	At onset: 600mg single dose (po)	300mg 2x/day (po) (for 1 week)	No	At 6 months: 18.0% vs 27.5% [Efficacy: 38%] At 15 months: 21.5% vs 30.6% [Efficacy: 30%]
Petra Trial:						
Arm A (n = 480)	Zidovudine + Lamivudine (3TC)	300mg 2x/day (po) (from week 36) 150mg 2x/day (po) (from week	300mg 3 hourly (po) 150mg 12 hourly (po)	300mg 2x/day (po) (for 1 week) 150mg 2x/day (po) (for 1	4mg/kg 2x/day (po) (for 1 week) 2mg/kg 2x/day (po)	At 6 weeks: 8.2% vs 19.1% [Efficacy: 57%] At 18 months: 21.3% vs 26.8%

Study	Drug (Patient no.)	Treatment				Transmission rate: Active vs placebo [Relative efficacy]
		Mother			Infant	
		Antepartum	Intrapartum	Postpartum		
		36)		week)	(for 1 week)	[Efficacy: 21.0%]
Arm B (n = 480)	Zidovudine + Lamivudine (3TC)	No No	300mg 3 hourly (po) 150mg 12 hourly (po)	300mg 2x/day (po) (for 1 week) 150mg 2x/day (po) (for 1 week)	4mg/kg 2x/day (po) (for 1 week) 2mg/kg 2x/day (po) (for 1 week)	At 6 weeks: 12.3% vs 19.1% [Efficacy: 36.0%] At 18 months: 24.9% vs 26.8% [Efficacy: 7.0%]

Post-Exposure Prophylaxis in adults following Occupational Exposure:
The best prophylaxis against occupational exposure is adherence to universal precautions including, amongst others, careful disposal of sharp objects e.g. needles and scalpels and the use of protective barriers (e.g. gloves, eyeglasses etc.).

Zidovudine in combination with lamivudine is indicated for initial prophylactic treatment (until results of serology tests are available) in HIV negative adults whenever there has been exposure to material known to be, or strongly suspected to be, infected with HIV. This includes:
- percutaneous injury (from needles, instruments, bone fragments, etc);
- exposure of broken skin (abrasions, cuts, eczema etc);
- exposure of mucous membranes including the eye.

Randomised clinical studies on the use of these products following occupational exposure have not

been performed. However, a retrospective case-controlled study has concluded that the use of zidovudine for post-exposure prophylaxis reduces the rate of infection. The use of zidovudine and lamivudine in combination has demonstrated a greater reduction in viral load than either drug used alone.

The addition of a protease inhibitor to the combination regimen is recommended in the following cases:
- when a large volume of inoculation has occurred;
- when the source material has a high viral titre; or
- when inoculation has occurred from a patient with HIV resistant to zidovudine and/or lamivudine.

DOSAGE AND ADMINISTRATION:

Dosage in Adults

The recommended dose of RETROVIR in combination with other antiretroviral agents is 500 or 600 mg/day in two or three divided doses. Monotherapy with dosages $\geq$ 1000 mg/day in divided doses have been used in earlier clinical trials. The effectiveness of dosages lower than 1000 mg/day in the treatment or prevention of HIV-associated neurological dysfunction is unknown. For dosages of antiretroviral agents used in combination therapy in advanced HIV infection please consult the package inserts of the individual agents.

Dosage in Children

3 months – 12 years:

The recommended dose of RETROVIR is 360 to 480 mg/m^2 per day, in 3 or 4 divided doses in combination with other antiretroviral agents. For the treatment or prevention of HIV-associated neurological dysfunction, the effectiveness of dosages less than 720 mg/m^2 per day (180 mg/m^2 every six hours) is unknown. The maximum dosage should not exceed 200 mg every six hours.

Dosage in the prevention of maternal-foetal transmission

The following dosage regimen has been shown to be effective. Pregnant women (over 14 weeks of gestation) should be given 500 mg/day orally (100 mg five times/daily) until the beginning of labour. During labour and delivery RETROVIR should be administered intravenously at 2 mg/kg bodymass given over 1 hour followed by a continuous intravenous infusion at 1 mg/kg/h until the umbilical cord is clamped. The newborn infants should be given Retrovir 2 mg/kg bodyweight orally every 6 hours starting within 12 hours after birth, and continuing until 6 weeks old. Infants unable to receive oral dosing should be given Retrovir intravenously at 1.5 mg/kg bodyweight infused over 30 minutes every 6 hours.

A randomised, placebo-controlled trial carried out in Thailand in collaboration with the Centres for Disease Control (CDC) has shown a 51 % reduction in the risk of transmission of HIV from mother to child (19 % infection rate for placebo vs. 9 % for zidovudine). Zidovudine was administered at the following doses:
36 weeks gestation to onset of labour: 300mg orally twice daily.
Onset of labour to delivery: 300mg orally every 3 hours.
No mothers in this study breast fed their infants.

For details on the studies carried out on mother-to-child transmission of HIV please refer to the table entitled 'Antiretroviral interventions to reduce MTCT of HIV of proven efficacy'.

Dosage adjustments in patients with haematological toxicity: Dosage reduction or interruption of zidovudine therapy may be necessary in patients whose haemoglobin level falls to between 7,5 g/dL (4,65 mmol/L) and 9 g/dL (5,59 mmol/L) or whose neutrophil count falls to between 0,75 x 10^9/L and 1,0 x 10^9/L.

Dosage adjustments in recipients of combination RETROVIR and other antiretroviral therapy: For recipients of combination zidovudine and other antiretroviral therapy, dosage adjustments for either drug 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 should also be interrupted or dose reduced. Physicians should refer to the

complete product information for the other antiretroviral agents for a description of known adverse reactions.

Dosage in the elderly: Zidovudine pharmacokinetics have not been studied in patients over 65 years of age and no specific data are available. 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. Appropriate monitoring of patients before and during use of zidovudine is advised.

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 but this does not appear to cause toxicity.
In patients with severe renal impairment on peritoneal or haemodialysis daily dosages of 300 – 400 mg in 3 – 4 divided dosages should be appropriate.
Haematological parameters and clinical response may influence the need for subsequent dosage adjustment. Haemodialysis and peritoneal dialysis have no significant effect on elimination of zidovudine but enhance the elimination of the glucuronide metabolite.

Dosage in hepatic impairment: 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, as there is only limited data available, precise recommendations cannot be made. Physicians will need to monitor for signs of intolerance and adjust the dose and/or increase the interval between doses as appropriate.

CONTRAINDICATIONS:
Zidovudine is contraindicated in patients known to be hypersensitive to zidovudine or to any of the components of the formulations.
Zidovudine should not be given to patients with abnormally low neutrophil cell counts (less than 0,75 x 10^9/L) or abnormally low haemoglobin levels (less than 7,5 g/dL). There is a known interaction between zidovudine and stavudine (d4T) (see INTERACTIONS). The concomitant use of these two agents should be avoided.

Children < 3 months: The limited data available are insufficient to propose specific dosage recommendations.

There is a known interaction between zidovudine and stavudine (see INTERACTIONS). The concomitant use of these two agents should be avoided.

WARNINGS AND PRECAUTIONS:
Patients should be cautioned about the concomitant use of self-administered medications (see INTERACTIONS).

Zidovudine is not a cure for HIV infection and patients remain at risk of developing illnesses which are associated with immune suppression, including opportunistic infections and neoplasms. Whilst it has been shown to reduce the risk of opportunistic infections, data on the development of neoplasms, including lymphomas are limited. In patients with early HIV disease on long-term treatment the risk of lymphoma development is unknown. Patients receiving combination therapy may also continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close observation of physicians experienced in the treatment of patients with HIV-associated diseases.

Pregnant women considering the use of zidovudine during pregnancy and labour for prevention of HIV transmission to their infants should be advised that transmission may still occur in some cases despite therapy.

Haematological adverse reactions:
Anaemia (usually occurring after 6 weeks of therapy but occasionally earlier), neutropaenia (usually occurring at any time after 4 weeks' therapy but sometimes earlier) and leucopaenia (usually secondary to neutropaenia) can be expected to occur frequently in patients receiving zidovudine. These occurred more frequently at higher dosages (1 200 to 1 500 mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease. Therefore haematological parameters should be carefully monitored. For patients with advanced symptomatic HIV disease it is generally recommended that blood tests are performed at least every 2 weeks for the first 3 months of therapy and at least monthly thereafter. In patients with early HIV disease (where bone marrow reserve is generally good), haematological toxicity is less frequent. Depending on the overall condition of the patient, blood tests may be performed less often, for example every 1 to 3 months. If the haemoglobin level falls to between 7,5 g/dL (4,65 mmol/L) and 9 g/dL (5,59 mmol/L) or the neutrophil count falls to between 0,75 x 10^9/L and 1,0 x 10^9/L, the daily dosage may be reduced until there is evidence of marrow recovery; alternatively, recovery may be enhanced by brief (2 to 4 weeks) interruption of zidovudine therapy. Marrow recovery is usually observed within 2 weeks after which time zidovudine therapy at a reduced dosage may be reinstituted. In patients with significant anaemia, dosage adjustments do not necessarily eliminate the need for transfusions (see CONTRAINDICATIONS).

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, in the treatment of HIV infection. 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).

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 RETROVIR 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.

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.

Patients co-infected with hepatitis C virus: Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. Therefore, the co-administration of ribavirin and zidovudine is not advised and consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This is particularly important in patients with a known history of zidovudine induced anaemia.

INTERACTIONS:

Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated metabolite. Medicines which are primarily eliminated by hepatic metabolism especially via glucuronidation may have the potential to inhibit metabolism of zidovudine. The interactions listed below should not be considered exhaustive but are representative of the classes of drug where caution should be exercised. Patients should be cautioned about the concomitant use of self-administered medications.

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

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

Lamivudine:
A modest increase in Cmax (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Phenytoin:
Phenytoin blood levels have been reported to be low in some patients receiving zidovudine, while in one patient a high level was noted. These observations suggest that phenytoin levels should be carefully monitored in patients receiving both drugs.

Probenecid:
Limited data suggest that probenecid increases the mean half-life and area under the plasma concentration curve of zidovudine, by decreasing glucuronidation. Renal excretion of glucuronide (and possibly zidovudine itself) is reduced in the presence of probenecid.
Rifampicin:
Limited data suggests that co-administration of zidovudine and rifampicin decreases the AUC of zidovudine by 48 % $\pm$ 34 %. However, the clinical significance of this is unknown.

Stavudine:
Zidovudine may inhibit the intracellular phosphorylation of stavudine when the two medicinal products are used concurrently. Zidovudine is therefore not recommended to be used in combination with stavudine (see CONTRA-INDICATIONS).

Miscellaneous:

Other drugs (such as aspirin, codeine, morphine, methadone, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and isoprinosine) may also alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibilities of interactions before using such medicines (particularly those impairing glucuronidation or directly inhibiting hepatic microsomal metabolism) especially in chronic therapy in combination.

Concomitant therapy with potentially nephrotoxic, or myelosuppressive medicines (e.g. dapsone, systemic pentamidine, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of toxicity with zidovudine**.** 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 both agents should be reduced.

Since some patients receiving zidovudine may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Limited data of oral RETROVIR do not indicate an increased risk of toxicity with co-trimoxazole, aerosolized pentamidine, pyrimethamine and acyclovir.

Please refer to the Pharmacokinetics in Adults section for details of the pharmacokinetics of zidovudine when administered with other antiretroviral agents.

PREGNANCY AND LACTATION:

Pregnancy

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 Clinical Studies).

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

Zidovudine has been shown to cross the placenta in humans (see Pharmacokinetics).

Zidovudine has been associated with findings in animal reproductive studies (see Non-Clinical Information). Pregnant women considering using RETROVIR during pregnancy should be made aware of these findings.

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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.

Maternal-foetal transmission

In study ACTG 076 the use of RETROVIR in pregnant women over 14 weeks of gestation, with subsequent treatment of their newborn infants, has been shown to significantly reduce the rate of maternal-foetal transmission of HIV (23% infection rate for placebo versus 8% for RETROVIR). Oral RETROVIR therapy began between weeks 14 and 34 of gestation and continued until onset of labour. During labour and delivery RETROVIR was administered intravenously. The newborn infants received RETROVIR orally until 6 weeks old. Infants unable to receive oral dosing were given the i.v. formulation.

In the 1998 Thailand CDC study, use of oral RETROVIR therapy only, from week 36 of gestation until delivery, significantly reduced the rate of maternal-foetal transmission of HIV (19% infection rate for placebo versus 9% for RETROVIR). No mothers in this study breast fed their infants.

It is unknown whether there are any long-term consequences of in utero and infant exposure to zidovudine. Based on the animal carcinogenicity/mutagenicity findings a carcinogenic risk to humans cannot be excluded (see Non-Clinical Information). The relevance of these findings to both infected and uninfected infants exposed to zidovudine is unknown. However, pregnant women considering using RETROVIR during pregnancy should be made aware of these findings.

Lactation
Health experts recommend that where possible women infected with HIV should not breast feed their infants in order to avoid the transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy. 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 dose of 300 mg zidovudine twice daily (given either as a single entity or as COMBIVIR or TRIZIVIR) the maternal plasma:breast milk ratio ranged between 0.4 and 3.2. Zidovudine median infant serum concentration was 24 ng/mL in one study and was below assay limit of quantification (30 ng/mL) in another study. Intracellular zidovudine triphosphate (active metabolite of zidovudine) levels in breastfed infants were not measured therefore the clinical relevance of the serum concentrations of the parent compound measured is unknown.

Effects on Ability to Drive and Use Machines
There have been no studies to investigate the effect of RETROVIR on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance. Nevertheless, the clinical status of the patient and the adverse event profile of RETROVIR should be borne in mind when considering the patient's ability to drive or operate machinery.

ADVERSE REACTIONS:

The adverse event profile appears similar for adults and children. The following events have been reported in patients treated with zidovudine. The following convention has been utilised for the classification of undesirable effects:-
Very common (> 1/10), common (> 1/100, <1/10), uncommon (> 1/1 000, < 1/100), rare (> 1/10 000, < 1/1 000) very rare (< 1/10 000).

Blood and lymphatic system disorders
Common: anaemia (which may require transfusion), neutropaenia and leucopaenia.

These occur more frequently at higher dosages (1 200 to 1 500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with low T4 (T-helper) cell counts (less than 100/mm^3). Dosage reduction or cessation of therapy may become necessary (see DOSAGE AND DIRECTIONS FOR USE). The incidence of neutropaenia was also increased in patients with pre-existing neutropaenia or anaemia, those with low vitamin B_{12} levels and those taking paracetamol concomitantly (see INTERACTIONS).

Uncommon: thrombocytopaenia and pancytopaenia (with marrow hypoplasia)
Rare: pure red cell aplasia
Very rare: aplastic anaemia

Metabolism and nutrition disorders
Common: hyperlactataemia
Rare: lactic acidosis (see Warnings and Precautions), anorexia
Treatment with zidovudine has been associated with loss of subcutaneous fat (see Warnings and Precautions).
Psychiatric disorders
Rare: anxiety and depression

Nervous system disorders
Very common: headache
Common: dizziness
Rare: insomnia, paraesthesiae, somnolence, loss of mental acuity, convulsions

Cardiac disorders
Rare: cardiomyopathy

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea
Rare: cough

Gastrointestinal disorders
Very common: nausea
Common: vomiting, abdominal pain, and diarrhoea
Uncommon: flatulence
Rare: oral mucosa pigmentation, taste disturbance and dyspepsia. Pancreatitis

Hepatobiliary disorders
Common: raised blood levels of liver enzymes and bilirubin
Rare: liver disorders such as severe hepatomegaly with steatosis

Skin and subcutaneous disorders
Uncommon: rash and pruritis
Rare: nail and skin pigmentation, urticaria and sweating

Musculoskeletal and connective tissue disorders
Common: myalgia
Uncommon: myopathy

Renal and urinary disorders
Rare: urinary infrequency

Reproductive system and breast disorders
Rare: gynaecomastia

General disorders and administration site conditions
Common: malaise
Uncommon: fever, generalised pain and asthenia
Rare: chills, chest pain and influenza-like syndrome.

The available data from placebo-controlled and open-label studies indicate that the incidence of nausea and other frequently reported clinical adverse events consistently decreases over time during the first few weeks of therapy with zidovudine.

OVERDOSE:

Symptoms and Signs
No specific symptoms or signs have been identified following acute overdose with zidovudine apart from those listed as side-effects.

Treatment
Patients should be observed closely for evidence of toxicity (see SIDE-EFFECTS AND SPECIAL PRECAUTIONS) and given the necessary supportive therapy. Haemodialysis appears to have a limited effect on elimination of zidovudine but enhances the elimination of the glucuronide metabolite.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group - nucleoside analogue - ATC Code J05A F01

Zidovudine is an antiviral agent active *in vitro* against retroviruses including the HIV. The HIV infection is unlikely to be completely eradicated by zidovudine treatment because the viral genome is integrated into the host DNA. Zidovudine is phosphorylated in both infected and uninfected cells to the monophosphate (MP) derivative by cellular thymidine kinase. Subsequent phosphorylation of zidovudine-MP to the diphosphate and then the triphosphate (TP) derivative is catalysed by cellular thymidylate kinase and nonspecific kinases, respectively. Zidovudine-TP acts as an inhibitor of and substrate for, the viral reverse transcriptase. The formation of further proviral DNA is blocked by incorporation of zidovudine-TP into the chain and subsequent chain termination. Competition by zidovudine-TP for HIV reverse transcriptase is approximately 100-fold greater than for cellular DNA polymerase alpha. No antagonistic effects in vitro were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine, lamivudine and interferon alpha).

Resistance to thymidine analogues (of which zidovudine is one) is well characterised and is conferred by the stepwise accumulation of up to six specific mutations in the HIV reverse transcriptase at codons 41, 67, 70, 210, 215 and 219. Viruses acquire phenotypic resistance to thymidine analogues through the combination of mutations at codons 41 and 215 or by the accumulation of at least four of the six mutations. These thymidine analogue mutations alone do not cause high-level cross-resistance to any of the other nucleosides, allowing for the subsequent use of any of the other approved reverse transcriptase inhibitors.

Two patterns of multi-drug resistance mutations, the first characterised by mutations in the HIV reverse transcriptase at codons 62, 75, 77, 116 and 151 and the second typically involving a T69S mutation plus a 6-base pair insert at the same position, result in phenotypic resistance to zidovudine as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

Reduced in vitro sensitivity to zidovudine has been reported for HIV isolates from patients who have received prolonged courses of RETROVIR 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 relationships between in vitro susceptibility of HIV to zidovudine and clinical response to therapy remain under investigation. In vitro susceptibility testing has not been standardised and results may therefore vary according to methodological factors.

Studies in vitro of zidovudine in combination with lamivudine indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. Evidence from clinical studies show that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior antiretroviral therapy. Zidovudine has been widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (nucleoside reverse transcriptase inhibitors) or different classes (protease inhibitors, non-nucleoside reverse transcriptase inhibitors).

Post-exposure prophylaxis (PEP):
Internationally recognised guidelines (Centre for Disease Control and Prevention - June 1998), recommend that in the event of accidental exposure to HIV infected blood e.g. from a needlestick injury, a combination of RETROVIR and EPIVIR™ should be administered promptly (within 1 to 2 h). In cases of higher risk of infection a protease inhibitor should be included in the regimen. It is recommended that antiretroviral prophylaxis be continued for four weeks. No controlled clinical studies have been carried out in post-exposure prophylaxis and supporting data is limited. Seroconversion may still occur despite prompt treatment with antiretroviral

agents.

PHARMACOKINETICS

Pharmacokinetics in adults: Zidovudine is well absorbed from the gut and, at all dose levels studied, the absolute bioavailability was 60 - 70 %. Mean steady state peak (Css max) and trough (Css min) plasma concentrations following oral doses of 5 mg/kg solution every four hours were 7,1 and 0,4 μM respectively (or 1,9 and 0,1 μg/ml). Limited data with RETROVIR Capsules suggest Css

max and Css min levels following a dose of 200 mg every four hours are about 3,5 and less than 0,5 μM (or about 1,0 and less than 0,1 μg/ml), respectively; the corresponding levels following a dosage of 250 mg every four hours are about 4,4 and 0,4 μM respectively (or 1,2 and 0,1 μg/ml).
From studies with intravenous zidovudine, the terminal plasma half-life was approximately 1,1 hours. Renal clearance of zidovudine greatly exceeds creatinine clearance, indicating that significant tubular secretion takes place. The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine and accounts for about 50 - 80 % of the administered dose eliminated by renal excretion. 3'amino-3'-deoxythymidine has been identified as a metabolite of zidovudine following intravenous dosing. No other metabolites have been observed.
Cerebrospinal fluid levels of zidovudine are approximately 50 % of corresponding plasma levels following chronic dosing. Plasma protein binding is relatively low (34 to 38 %). There are limited data concerning the pharmacokinetics of zidovudine in patients with renal or hepatic impairment. No data are available on the pharmacokinetics of zidovudine in the elderly.
In patients on chronic dialysis, doses of 300 mg/day in divided dosages resulted in plasma levels similar to those of normal volunteers on 500 – 600 mg/day.
Co-administration of lamivudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.
Pharmacokinetics of zidovudine when used in combination with other anti-retroviral agents:
Data from pharmacokinetic/drug interaction studies indicate that there were no clinically significant alterations to zidovudine pharmacokinetics when given concomitantly with the following anti-retroviral agents:

Nucleoside reverse transcriptase inhibitors (NRTIs): zalcitabine, didanosine and abacavir;
Non-nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine and efavirenz; and
Protease inhibitors: indinavir sulphate, saquinavir mesylate, ritonavir, amprenavir and nelfinavir.
Zidovudine administration does not result in any clinically significant alterations to the pharmacokinetics of the above listed agents when given concomitantly.
There is a known interaction between zidovudine and stavudine (d4T) (see INTERACTIONS). The concomitant use of these two agents should be avoided.

Administration of co-trimoxazole with the zidovudine/lamivudine combination in patients with renal impairment should be carefully assessed.

Pharmacokinetics in children: Zidovudine clearance is significantly reduced in children less than one month of age.
In children over the age of five 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 the bioavailability was 60 - 74 % with a mean of 65 %. Css max levels were 4,45 μM (1,19 μg/ml) following a dose of 120 mg zidovudine (in solution) /m^2 body surface area and 7,7 μM (2,06 μg/ml) at 180 mg/m^2 body surface area.

In children, the mean cerebrospinal fluid/plasma zidovudine concentration ratio ranged from 0.52 to 0.85, as determined during oral therapy 0.5 to 4 h after dosing and was 0.87 as determined during i.v. therapy 1 to 5 h after a 1 h infusion. During continuous i.v. infusion, the mean steady-state cerebrospinal fluid/plasma concentration ratio was 0.24.

With intravenous dosing, the mean terminal plasma half-life and total body clearance were 1,5 hours and 30,9 ml/min/kg respectively. The major metabolite is the 5'–glucuronide. After intravenous dosing, 29 % of the dose was recovered unchanged in the urine and 45 % excreted as the glucuronide. Renal clearance of zidovudine greatly exceeds creatinine clearance indicating that significant tubular secretion takes place. The limited data available on the pharmacokinetics in neonates and young infants indicate that glucuronidation of zidovudine is reduced with a consequent increase in bioavailability, reduction in clearance and longer half-life in infants less than 14 days old, but thereafter the pharmacokinetics appear similar to those reported in adults.

Pharmacokinetics in pregnancy: The pharmacokinetics of zidovudine in eight women during

the last trimester of pregnancy were similar to that of non-pregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in infant plasma at birth were essentially equal to those in maternal plasma at delivery. The elimination half-life in newborn infants was 13,8 hours.

CLINICAL STUDIES

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.

NON-CLINICAL INFORMATION

Reproductive toxicology: In animal studies, zidovudine was shown to cross the placenta, and have demonstrated evidence of causing an increase in early embryonic deaths in rats and rabbits. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations. No evidence of teratogenicity has been observed at lower doses tested.

Carcinogenicity and mutagenicity: Based on the animal and mutagenicity findings, a carcinogenic risk cannot be excluded. Although the predictive value of rodent carcinogenic studies for humans is uncertain, late-occurring vaginal tumours appearing after 19 months of continuous daily oral dosing have been seen in rodents following lifetime dosing with zidovudine. A pilot study has demonstrated that zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. The relevance of these findings to both infected and uninfected infants exposed to zidovudine is not known. However, pregnant women considering using zidovudine should be made aware of these findings.

IDENTIFICATION:

A clear, pale yellow syrup with the odour of strawberries.

PRESENTATION:

Glass bottle of 200 ml syrup, packed in a carton. The carton will also contain a plastic syringe adaptor and a 1 mL plastic oral-dosing syringe with 0.1 mL increments OR a 10mL plastic oral-dosing syringe with 0.2mL increments which are individually shrink wrapped in clear plastic.

STORAGE INSTRUCTIONS:

Syrup: Keep out of the reach of children.
Store below 30 °C.
Protect from light.

REGISTRATION NUMBERS:
Botswana: BOT0500819 S2
Namibia: 04/20.2.8/0902 NS2
Malawi: PMPB/PL270/48 POM
Zimbabwe: 99/7.13/3555 PP

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATES:
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