RETROVIR CAPSULES 250 MG

1. NAME OF THE MEDICINAL PRODUCT

Retrovir 250 mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg zidovudine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard

Hard gelatin capsules with opaque blue cap and opaque white body coded GSJV2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Retrovir oral formulations are indicated in anti-retroviral combination therapy for Human Immunodeficiency Virus (HIV) infected adults and children.

Retrovir chemoprophylaxis is indicated for use in HIV-positive pregnant women (over 14 weeks of gestation) for prevention of maternal-foetal HIV transmission and for primary prophylaxis of HIV infection in newborn infants.

4.2 Posology and method of administration

Retrovir should be prescribed by physicians who are experienced in the treatment of HIV infection.

Dosage in adults and adolecents weighing at least 30 kg: The usual recommended dose of Retrovir in combination with other anti-retroviral agents is 250 or 300 mg twice daily.

Dosage in children: Retrovir 100 mg capsules and Retrovir 100 mg/10 ml oral solution are available for use in children.

Weight (kg)	**In the morning**	**In the evening**	**Daily dose (mg)**
8-13	one 100 mg capsule	one 100 mg capsule	200
14-21	one 100 mg capsule	two 100 mg capsules	300
22-30	two 100 mg capsules	two 100 mg capsules	400

Alternatively children weighing at least 28 kg to 30 kg (included) could take:			
28-30	one 250 mg capsule	one 250 mg capsule	500

Oral solution is available for dosing children less than 8 kg and for those children above 8 kg unable to swallow capsules (see Oral Solution SPC).

Dosage in the prevention of maternal-foetal transmission: Pregnant women (over 14 weeks of gestation) should be given 500 mg/day orally (100 mg five times per day) until the beginning of labour. During labour and delivery Retrovir should be administered intravenously at 2 mg/kg bodyweight given over one hour followed by a continuous intravenous infusion at 1 mg/kg/h until the umbilical cord is clamped.

Neonates should be given 0.2 mL/kg (2 mg/kg) bodyweight orally every 6 hours starting within 12 hours after birth and continuing until 6 weeks old.

Care should be taken when calculating doses for neonates due to the small volumes of oral solution required. To facilitate dosing precision, an appropriately sized syringe with 0.1 mL graduation should be used to ensure accurate oral dosing of neonates (see oral solution SPC).

Infants unable to receive oral dosing should be given Retrovir intravenously at 1.5 mg/kg bodyweight infused over 30 minutes every 6 hours.

In case of planned caesarean, the infusion should be started 4 hours before the operation. In the event of a false labour, the Retrovir infusion should be stopped and oral dosing restarted.

Dosage adjustments in patients with haematological adverse reactions: Substitution of zidovudine should be considered in patients whose haemoglobin level or neutrophil count fall to clinically significant levels. Other potential causes of anaemia or neutropenia should be excluded. Retrovir dose reduction or interruption should be considered in the absence of alternative treatments (see sections 4.3 and 4.4).

Dosage in the elderly: Zidovudine pharmacokinetics have not been studied in patients over 65 years of age and no specific data are available. However, since 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 Retrovir is advised.

Dosage in renal impairment: The recommended dose for patients with severe renal impairment (creatinine clearance < 10 ml/min) and patients with end-stage renal disease maintained on haemodialysis or peritoneal dialysis is 100 mg every 6 to 8 hrs (300-400 mg daily). Haematological parameters and clinical response may influence the need for subsequent dosage adjustment (see section 5.2).

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 reductions may be necessary but, due to the large variability in zidovudine exposures in patients with moderate to severe liver disease, precise recommendations cannot be made. If monitoring of plasma zidovudine levels is not feasible, physicians will need to monitor for signs of intolerance, such as the development of haematological adverse reactions (anaemia, leucopenia, neutropenia) and reduce the dose and/or increase the interval between doses as appropriate (see section 4.4).

4.3 Contraindications

Retrovir Oral Formulations are contra-indicated in patients known to be hypersensitive to zidovudine, or to any of the excipients listed in section 6.1.

Retrovir Oral Formulations should not be given to patients with abnormally low neutrophil counts (less than 0.75 x 10^9/litre) or abnormally low haemoglobin levels (less than 7.5 g/decilitre or 4.65 mmol/litre).

Retrovir is contra-indicated in new born infants with hyperbilirubinaemia requiring treatment other than phototherapy, or with increased transaminase levels of over five times the upper limit of normal.

4.4 Special warnings and precautions for use

Retrovir is not a cure for HIV infection or AIDS. Patients receiving Retrovir or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection.

The concomitant use of rifampicin or stavudine with zidovudine should be avoided (see section 4.5).

Haematological Adverse Reactions: Anaemia (usually not observed before six weeks of Retrovir therapy but occasionally occurring earlier), neutropenia (usually not observed before four weeks' therapy but sometimes occurring earlier) and leucopenia (usually secondary to neutropenia) can be expected to occur in patients receiving Retrovir; These occurred more frequently at higher dosages (1200-1500 mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease (see section 4.8).

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 two weeks for the first three months of therapy and at least monthly thereafter. 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 (2-4 weeks) interruption of Retrovir therapy. Marrow recovery is usually observed within 2 weeks after which time Retrovir therapy at a reduced dosage may be reinstituted. In patients with significant anaemia, dosage adjustments do not necessarily eliminate the need for transfusions (see section 4.3).

Lactic acidosis: lactic acidosis usually associated with hepatomegaly and hepatic steatosis has been reported with the use of zidovudine. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with zidovudine should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering zidovudine to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

Mitochondrial dysfunction following exposure in utero: Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasaemia). These events have often been transitory. Late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

*Lipoatrophy:*Treatment with zidovudine has been associated with loss of subcutaneous fat, which has been linked to mitochondrial toxicity. 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 not be reversible when switching to a zidovudine-free regimen. Patients should be regularly assessed for signs of lipoatrophy during therapy with zidovudine and zidovudine-containing products (Combivir and Trizivir). Therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy development.

*Weight and metabolic parameters:*An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Liver disease: Zidovudine clearance in patients with mild hepatic impairment without cirrhosis [Child-Pugh scores of 5-6] is similar to that seen in healthy subjects, therefore no zidovudine dose adjustment is required. In patients with moderate to severe liver disease [Child-Pugh scores of 7-15], specific dosage recommendations cannot be made due to the large variability in zidovudine exposure observed, therefore zidovudine use in this group of patients is not recommended.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please also refer to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening

liver disease in such patients, interruption or discontinuation of treatment must be considered (see section 4.2).

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens 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 CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Patients should be cautioned about the concomitant use of self-administered medications (see section 4.5).

Use in Elderly and in Patients with Renal or Hepatic Impairment: see section 4.2.

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

Patients co-infected with hepatitis C virus: The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

Excipients:
Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Limited data suggests that co-administration of zidovudine with rifampicin decreases the AUC (area under the plasma concentration curve) of zidovudine by 48% ± 34%. This may result in a partial loss or total loss of efficacy of zidovudine. The concomitant use of rifampicin with zidovudine should be avoided (see section 4.4).

Zidovudine in combination with stavudine is antagonistic in vitro. The concomitant use of stavudine with zidovudine should be avoided (see section 4.4).

Probenecid increases the AUC of zidovudine by 106% (range 100 to 170%). Patients receiving both drugs should be closely monitored for haematological toxicity.

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

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

Valproic acid, fluconazole or methadone when co-administered with zidovudine have been shown to increase the AUC with a corresponding decrease in its clearance. As only limited data are available the clinical significance of these findings is unclear but if zidovudine is used concurrently with either valproic acid, fluconazole or methadone, patients should be monitored closely for potential toxicity of zidovudine.

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. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive drugs (eg. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine. If concomitant therapy with 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.

Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole, aerosolised pentamidine, pyrimethamine and aciclovir at doses used in prophylaxis.

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

4.6 Pregnancy and lactation

Pregnancy:
As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data (see section 5.3) as well as the clinical experience in pregnant women should be taken into account. In the present case, the use in pregnant women of zidovudine, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal-foetal transmission of HIV.

A large amount of data on pregnant women (more than 3000 outcomes from first trimester and more than 3000 outcomes from second and third trimester exposure) indicate no malformative toxicity. Retrovir can be used during pregnancy if clinically needed. The malformative risk is unlikely in humans based on the mentioned large amount of data.

Zidovudine has been associated with reproductive toxicity findings in animal studies (see section 5.3). The active ingredients of Retrovir may inhibit cellular DNA replication and zidovudine has been shown to be a transplacental carcinogen in one animal study. The clinical relevance of these findings is unknown. Placental transfer of zidovudine has been shown to occur in humans.

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 (see section 4.4).

Fertility:
Zidovudine did not impair male or female fertility in rats given oral doses of up to 450 mg/kg/day. There are no data on the effect of Retrovir on human female fertility. In men, Retrovir has not been shown to affect sperm count, morphology or motility.

Breast-feeding:
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. It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

4.7 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. Furthermore, 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 reaction profile of Retrovir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The adverse reaction profile appears similar for adults and children. The most serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia. These occurred more frequently at higher dosages (1200-1500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4 cell counts less than 100/mm^3. Dosage reduction or cessation of therapy may become necessary (see section 4.4).

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 Retrovir therapy.

The following events have been reported in patients treated with Retrovir.
The adverse events considered at least possibly related to the treatment (adverse drug reactions, ADR) are listed below by body system, organ class and absolute frequency. Frequencies are defined as Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000)and Very rare (<1/10,000).

Blood and lymphatic system disorders
Common: Anaemia, neutropenia and leucopenia
Uncommon: Pancytopenia with bone marrow hypoplasia, thrombocytopenia
Rare: Pure red cell aplasia
Very rare: Aplastic anaemia

Metabolism and nutrition disorders

Rare: Lactic acidosis in the absence of hypoxaemia, anorexia

Psychiatric disorders
Rare: Anxiety and depression

Nervous system disorders
Very common: Headache
Common: Dizziness
Rare: Convulsions, loss of mental acuity, insomnia, paraesthesia, somnolence

Cardiac disorders
Rare: Cardiomyopathy

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea
Rare: Cough

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting, diarrhoea and abdominal pain
Uncommon: Flatulence
Rare: Pancreatitis. Oral mucosa pigmentation, taste disturbance and dyspepsia.

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

Skin and subcutaneous tissue disorders
Uncommon: Rash and pruritis
Rare: Urticaria, nail and skin pigmentation, and sweating

Musculoskeletal and connective tissue disorders
Common: Myalgia
Uncommon: Myopathy

Renal and urinary disorders
Rare: Urinary frequency

Reproductive system and breast disorders
Rare: Gynaecomastia

General disorders and administration site disorders
Common: Malaise
Uncommon: Asthenia, fever, and generalised pain
Rare: Chest pain and influenza-like syndrome, chills

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

Adverse reactions with Retrovir for the prevention of maternal-foetal transmission:

In a placebo-controlled trial, overall clinical adverse reactions and laboratory test abnormalities were similar for women in the Retrovir and placebo groups. However, there

was a trend for mild and moderate anaemia to be seen more commonly prior to delivery in the zidovudine treated women.

In the same trial, haemoglobin concentrations in infants exposed to Retrovir for this indication were marginally lower than in infants in the placebo group, but transfusion was not required. Anaemia resolved within 6 weeks after completion of Retrovir therapy. Other clinical adverse reactions and laboratory test abnormalities were similar in the Retrovir and placebo groups. It is unknown whether there are any long-term consequences of in utero and infant exposure to Retrovir.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of zidovudine (see section 4.4).

Treatment with zidovudine has been associated with loss of subcutaneous fat which is most evident in the face, limbs and buttocks. Patients receiving Retrovir should be frequently examined and questioned for signs of lipoatrophy. When such development is found, treatment with Retrovir should not be continued (see section 4.4).

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

Symptoms and signs:
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) and given the necessary supportive therapy.
Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine but enhance the elimination of the glucuronide metabolite.
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside analogue , ATC code: J05A F01

Mode of action:
Zidovudine is an antiviral agent which is highly active in vitro against retroviruses including the Human Immunodeficiency Virus (HIV).

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 (DP), and then the triphosphate (TP) derivative is catalysed by cellular thymidylate kinase and non-specific 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-MP 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.

Clinical virology:
The relationships between in vitro susceptibility of HIV to zidovudine and clinical response to therapy remain under investigation. In vitro sensitivity testing has not been standardised and results may therefore vary according to methodological factors. 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 reduction of sensitivity with the emergence of zidovudine resistant strains limits the usefulness of zidovudine monotherapy clinically. In clinical studies, clinical end-point data indicate that zidovudine, particularly in combination with lamivudine, and also with didanosine or zalcitabine results in a significant reduction in the risk of disease progression and mortality. The use of a protease inhibitor in a combination of zidovudine and lamivudine, has been shown to confer additional benefit in delaying disease progression, and improving survival compared to the double combination on its own.

The anti-viral effectiveness in vitro of combinations of anti-retroviral agents are being investigated. Clinical and in vitro studies of zidovudine in combination with lamivudine indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. Furthermore there is clinical evidence that zidovudine plus lamivudine delays the emergence of zidovudine resistance in anti-retroviral naive patients.

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 involving a T69S mutation plus a 6-base pair insert at the same position, result in phenotypic resistance to AZT as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

In the US ACTGO76 trial, Retrovir was shown to be effective in reducing the rate of maternal-foetal transmission of HIV-1 (23% infection rate for placebo versus 8% for zidovudine) when administered (100 mg five times a day) to HIV-positive pregnant women (from week 14-34 of pregnancy) and their newborn infants (2 mg/kg every 6 hours) until 6 weeks of age. In the shorter duration 1998 Thailand CDC study, use of oral Retrovir therapy only (300 mg twice daily), from week 36 of pregnancy until delivery, also reduced the rate of maternal-foetal transmission of HIV (19% infection rate for placebo versus 9% for zidovudine). These data, and data from a published study comparing zidovudine regimens to prevent maternal-foetal HIV transmission have shown that short maternal treatments (from week 36 of pregnancy) are less efficacious than longer maternal treatments (from week 14-34 of pregnancy) in the reduction of perinatal HIV transmission.

5.2 Pharmacokinetic properties

Adults:

Absorption:
Zidovudine is well absorbed from the gut and, at all dose levels studied, the bioavailability was 60-70%. From a bioequivalence study, steady-state mean (CV%) C[ss]max, C[ss]min, and AUC[ss] values in 16 patients receiving zidovudine 300 mg tablets twice daily were 8.57 (54%) microM (2.29 μg/ml), 0.08 (96%) microM (0.02 μg/ml), and 8.39 (40%) h*microM (2.24 h*μg/ml), respectively.

Distribution:
From studies with intravenous Retrovir, the mean terminal plasma half-life was 1.1 hours, the mean total body clearance was 27.1 ml/min/kg and the apparent volume of distribution was 1.6 Litres/kg.

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

Plasma protein binding is relatively low (34 to 38%) and drug interactions involving binding site displacement are not anticipated.

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

Elimination:
Renal clearance of zidovudine greatly exceeds creatinine clearance, indicating that significant tubular secretion takes place.

Paediatrics:

Absorption:
In children over the age of 5-6 months, the pharmacokinetic profile of zidovudine is similar to that in adults. Zidovudine is well absorbed from the gut and, at all dose levels studied, its bioavailability was 60-74% with a mean of 65%. C^{ss}max levels were 4.45µM (1.19 µg/ml) following a dose of 120 mg Retrovir (in solution)/m^2 body surface area and 7.7 µM (2.06 µg/ml) at 180 mg/m^2 body surface area. Dosages of 180 mg/m^2 four times daily in children produced similar systemic exposure (24 hour AUC 40.0 hr µM or 10.7 hr µg/ml) as doses of 200 mg six times daily in adults (40.7 hr µM or 10.9 hr µg/ml).

Distribution:
With intravenous dosing, the mean terminal plasma half-life and total body clearance were 1.5 hours and 30.9 ml/min/kg respectively.

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

Biotransformation:
The major metabolite is 5‘-glucuronide. After intravenous dosing, 29% of the dose was recovered unchanged in the urine and 45% excreted as the glucuronide.

Elimination:
Renal clearance of zidovudine greatly exceeds creatinine clearance indicating that significant tubular secretion takes place.

The 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.

Pregnancy:
The pharmacokinetics of zidovudine has been investigated in a study of eight women during the third trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine was 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.

Elderly:
No specific data are available on the pharmacokinetics of zidovudine in the elderly.

Renal impairment:
In patients with severe renal impairment, apparent zidovudine clearance after oral zidovudine administration was approximately 50% of that reported in healthy subjects with normal renal function. Haemodialysis and peritoneal dialysis have no significant effect on zidovudine elimination whereas elimination of the inactive glucuronide metabolite is increased (see section 4.2).

Hepatic impairment:

There are limited data on the pharmacokinetics of zidovudine in patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Mutagenicity:
No evidence of mutagenicity was observed in the Ames test. However, zidovudine was weakly mutagenic in a mouse lymphoma cell assay and was positive in an in vitro cell transformation assay. Clastogenic effects were observed in an in vitro study in human lymphocytes and in in vivo oral repeat dose micronucleus studies in rats and mice. An in vivo cytogenetic study in rats did not show chromosomal damage. A study of the peripheral blood lymphocytes of eleven AIDS patients showed a higher chromosome breakage frequency in those who had received Retrovir than in those who had not. 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. A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed in utero to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

Carcinogenicity:
In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. A subsequent intravaginal carcinogenicity study confirmed the hypothesis that the vaginal tumours were the result of long term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine. There were no other drug-related tumours observed in either sex of either species.

In addition, two transplacental carcinogenicity studies have been conducted in mice. One study, by the US National Cancer Institute, administered zidovudine at maximum tolerated doses to pregnant mice from day 12 to 18 of gestation. One year post-natally, there was an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight).

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months, with exposure beginning prenatally on gestation day 10. Treatment related findings were limited to late-occurring vaginal epithelial tumours, which were seen with a similar incidence and time of onset as in the standard oral carcinogenicity study. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.

It is concluded that the transplacental carcinogenicity data from the first study represents a hypothetical risk, whereas the reduction in risk of maternal transfection of HIV to the uninfected child by the use of zidovudine in pregnancy has been well proven.

Reproductive Toxicity:
Studies in pregnant rats and rabbits given zidovudine orally at dosage levels up to 450 and 500 mg/kg/day respectively during the major period of organogenesis have revealed no evidence of teratogenicity. There was, however, a statistically significant increase in foetal resorptions in rats given 150 to 450 mg/kg/day and in rabbits given 500 mg/kg/day.

A separate study, reported subsequently, found that rats given a dosage of 3000 mg/kg/day, which is very near the oral median lethal dose (3683 mg/kg), caused marked maternal toxicity and an increase in the incidence of foetal malformations. No evidence of teratogenicity was observed in this study at the lower dosages tested (600 mg/kg/day or less).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core:
Maize starch
Microcrystalline Cellulose
Sodium Starch Glycollate
Magnesium Stearate.

Capsule coating:
Gelatin
E171 Titanium dioxide
Indigo carmine E132

Printing ink (black inks opacode 10A1 or 10A2):
Shellac
Black Iron Oxide E172
Propylene glycol
Ammonium hydroxide, 28% (in black ink opacode 10A1 only)
Strong Ammonium solution (in black ink opacode 10A2 only)
Potassium hydroxide (in black ink opacode 10A2 only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the label and packaging

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/aluminium foil blister pack containing 40 capsules.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MANUFACTURER

ViiV Healthcare UK Limited, London, UK

8. LICENCE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd. 25 Basel St., Petach Tikva

9. LICENCE NUMBER

024-28-25361

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