

RETROVIR IV

Zidovudine

QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 20 ml contains zidovudine 200 mg

IDENTIFICATION:

A clear, colourless or pale-yellow, sterile aqueous solution.

CLINICAL INFORMATION:

INDICATIONS:

RETROVIR IV is indicated for the short-term management of serious manifestations of Human Immunodeficiency Virus (HIV) infections in patients who are unable to take zidovudine oral formulations.

RETROVIR is indicated in pregnancy to reduce the rate of maternal-foetal transmission of HIV.

DOSAGE AND ADMINISTRATION:

The required dose of RETROVIR IV must be administered by slow i.v. infusion over a 1 h period. It must NOT be given intramuscularly.

Dosage in adults:

A dose of RETROVIR IV for infusion of 1,9 mg zidovudine/kg every 4 h (or 800 mg/day) is generally recommended for a 70 kg patient. This provides similar exposure (AUC) to an oral dose of approximately 2,9 mg zidovudine/kg every 4 h (or 1 200 mg/day) for a 70 kg patient. Patients should receive RETROVIR IV for infusion only until oral therapy can be administered.

In individual cases, medical practitioners may wish to select a lower dosage, depending on relevant factors such as the degree of bone marrow reserve of the patient. The effectiveness of less frequent dosing remains to be established.

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 $0,75 \times 10^9/l$ and $1,0 \times 10^9/l$.

Dosage in children:

Limited data are available on the use of RETROVIR IV in children.

Prevention of maternal-foetal transmission:

The following dosage regimen has been shown to be effective (see PREGNANCY AND LACTATION). 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 h, followed by a continuous i.v. infusion at 1 mg/kg/h until the umbilical cord is clamped.

Neonates should be given RETROVIR 0.2 mL/kg (2 mg/kg) bodyweight of oral solution every 6 h starting within 12 h after birth and continuing until 6 weeks old. Please see product information for RETROVIR oral solution. Infants unable to receive oral dosing should be given RETROVIR infusion intravenously at 1,5 mg/kg bodyweight infused over 30 minutes every 6 h.

Dosage in the elderly:

RETROVIR 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 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:

Compared to healthy subjects, patients with advanced renal failure have a 50 % higher maximum plasma concentration of RETROVIR. 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 a 400 mg in 3 a 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 RETROVIR 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. Medical practitioners will need to monitor for signs of intolerance and adjust the dose and/or increase the interval between doses as appropriate.

CONTRAINDICATIONS:

RETROVIR IV is contraindicated in patients known to be hypersensitive to zidovudine, or to any components of the formulation. RETROVIR IV should not be given to patients with abnormally low neutrophil cell counts (less than $0,75 \times 10^9$ /litre) 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.

WARNINGS AND PRECAUTIONS:

Patients should be cautioned about the concomitant use of self-administered medications (see INTERACTIONS). RETROVIR IV contains no preservative. Dilution should be carried out immediately before use and any unused solution should be discarded.

RETROVIR IV 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.

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 despite therapy.

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 RETROVIR, particularly to those with known risk factors for liver disease. Treatment with RETROVIR 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).

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. Apart from lactic acidosis/hyperlactataemia (see above) other

manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia) and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Pancreatitis:

Pancreatitis has been observed in some patients receiving RETROVIR. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of RETROVIR until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment:

In patients with moderate to severe renal impairment, the terminal half-life of RETROVIR is increased due to decreased clearance. The dose of RETROVIR should therefore be adjusted (see DOSAGE AND ADMINISTRATION).

Liver disease:

Use of RETROVIR can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of RETROVIR has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines.

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. If there is evidence of worsening liver disease in such

patients, temporary or permanent discontinuation of treatment must be considered.

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 tuberculosis, cytomegalovirus retinitis, other generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* (*P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Grave's 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 with HIV and hepatitis B or C virus co-infection:

Patients with chronic hepatitis B or C and treated with anti-retroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue RETROVIR should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post treatment exacerbation of hepatitis may lead to hepatic decompensation.

Exacerbation of anaemia due to ribavirin has been reported when RETROVIR is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated.

Therefore, the co-administration of ribavirin and RETROVIR is not advised and consideration should be given to replacing RETROVIR in a combination ART regimen if this is already established. This is particularly important in patients with a known history of RETROVIR induced anaemia.

Latex allergy:

The rubber stopper of the RETROVIR I.V. for infusion vials contains dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

Osteonecrosis:

Although the aetiology 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.

Opportunistic infections:

Patients receiving RETROVIR should be advised that they may continue to develop opportunistic infections and other complications of HIV infection and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:

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.

Haematological side effects:

Anaemia (usually occurring after six weeks of therapy but occasionally earlier), neutropenia (usually occurring at any time after 4 weeks' therapy but sometimes earlier) and leucopenia (usually secondary to neutropenia) can be expected to occur frequently in patients receiving RETROVIR. These occurred more frequently at higher dosages (1 200-1 500 mg/day) and in patients with poor bone marrow reserve prior to treatment and with advanced HIV disease. Haematological parameters should be carefully monitored. It is generally recommended that blood tests are performed at least weekly in patients receiving RETROVIR IV for infusion.

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 $0,75 \times 10^9/\ell$ and $1,0 \times 10^9/\ell$, 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 re-instituted. Data on the use of intravenous RETROVIR for periods in excess of 2 weeks are limited. In patients with significant anaemia, dosage adjustments do not necessarily eliminate the need for transfusions (see CONTRAINDICATIONS).

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. Zidovudine given to rats during organogenesis resulted in an increased incidence of malformations. RETROVIR should not be used in the first trimester of pregnancy.

Prevention of maternal-foetal transmission:

In placebo-controlled trials, haemoglobin concentrations in infants exposed to RETROVIR for this indication were lower than in infants in the placebo group, but transfusion was not required. Anaemia resolved within 6 weeks after completion of RETROVIR therapy. The long-term consequences of in utero and infant exposure to RETROVIR are unknown.

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.

Atovaquone: RETROVIR does not appear to affect the pharmacokinetics of atovaquone. However, pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of RETROVIR 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 RETROVIR 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 (*Pneumocystis carinii/jirovecii* pneumonia) would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of RETROVIR. Extra care should be taken in monitoring patients receiving prolonged atovaquone therapy.

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

Phenytoin: 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 medicines.

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

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 the glucuronide (and possibly zidovudine itself) is reduced in the presence of probenecid.

Rifampicin: limited data suggests that co-administration of RETROVIR and rifampicin decreases the AUC of zidovudine by 48 % \pm 34 %. However, the clinical significance of this is unknown.

Lamivudine: A modest increase in C_{max} (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.

Miscellaneous: other medicines (such as aspirin, codeine, morphine, methadone, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate,

dapsone and isoprinosine) may alter the metabolism of RETROVIR by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibilities of medicines interactions before using such medicines, particularly for chronic therapy, in combination with RETROVIR IV for infusion. Concomitant therapy with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, dapsone, pyrimethamine, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of toxicity with RETROVIR IV for infusion. If concomitant therapy with any of these medicines is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced. Since some patients receiving zidovudine may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Such therapy has included co-trimoxazole, aerosolised pentamidine, pyrimethamine and acyclovir. Limited data from clinical trials do not indicate a significantly increased risk of toxicity with these drugs.

PREGNANCY AND LACTATION:

Fertility

There are no data on the effect of RETROVIR on human female fertility. In men, oral zidovudine has been shown to have no effect on sperm count, morphology or motility.

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.

The safety of zidovudine for the mother and foetus during the first trimester of pregnancy has not been established.

Zidovudine is teratogenic in animals (see WARNINGS AND PRECAUTIONS). RETROVIR should not be used in the first trimester of pregnancy.

Zidovudine has been associated with findings in animal reproductive studies. Pregnant women considering using RETROVIR during pregnancy should be made aware of these findings.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peripartum to nucleoside reverse transcriptase inhibitors (NRTIs) such as RETROVIR. The clinical relevance of these elevations in serum lactate is unknown. There have also been reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and RETROVIR exposure *in utero* or peripartum has not been established.

Lactation

Women infected with HIV should not breastfeed 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.

Zidovudine is excreted in breast milk. In other studies following repeat oral dose of 300 mg zidovudine twice daily (given either as a single entity or as Lamivudine-Zidovudine or Abacavir-Lamivudine-Zidovudine) 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. RETROVIR causes dizziness and loss of mental activity that might interfere with ability to drive or operate machinery.

ADVERSE REACTIONS:

The following events have been reported in patients treated with RETROVIR.

The following convention has been utilised for the classification of undesirable effects:

Very common ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1\ 000, < 1/100$), rare ($\geq 1/10\ 000, < 1/1\ 000$) very rare ($< 1/10\ 000$).

Blood and lymphatic system disorders

Common: anaemia (which may require transfusion), neutropenia and leucopenia.
Dosage reduction or cessation of therapy may become necessary (see DOSAGE AND ADMINISTRATION). The incidence of neutropenia was also increased in patients with pre-existing neutropenia or anaemia and those with low vitamin B₁₂ levels.

Uncommon: thrombocytopenia and pancytopenia (with marrow hypoplasia)

Rare: pure red cell aplasia

Very rare: aplastic anaemia

Metabolism and nutrition disorders

Common: hyperlactataemia

Rare: lactic acidosis (see WARNINGS AND PRECAUTIONS), anorexia

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 pruritus

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.

OVERDOSE:

Symptoms and Signs:

No specific symptoms or signs have been identified following acute overdose with RETROVIR apart from those listed as side effects.

Treatment:

Patients should be observed closely for evidence of toxicity (see ADVERSE REACTIONS) 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:

Pharmacodynamic properties:

Pharmacotherapeutic group - nucleoside analogue - ATC Code J05A F01

Zidovudine is a nucleoside reverse-transcriptase inhibitor (NRTI). Zidovudine is an antiviral agent which is active *in vitro* against retroviruses including HIV, also known as HTLV-III or LAV. 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.

RETROVIR in combination with other ARVs

Resistance to zidovudine develops *in vitro* and *in vivo* with zidovudine monotherapy.

No antagonistic effects *in vitro* were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine, lamivudine and interferon-alpha). The relationship between the *in vitro* susceptibility of HIV to reverse transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

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. Furthermore *in vivo* there is clinical evidence that zidovudine plus lamivudine delays the emergence of zidovudine resistance in anti-retroviral naïve patients.

Pharmacokinetic properties:

Dose independent kinetics were observed in adult patients receiving one hour infusions of 1 to 5 mg/kg three to six times daily. Total body clearance was 1 900 ml/min/kg and 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 dose eliminated by renal excretion. No other metabolites have been observed. Mean steady state peak ($C_{ss_{max}}$) and trough ($C_{ss_{min}}$) plasma concentrations in adults following a one-hour infusion of 2,5 mg/kg every 4 hours were 4,0 and 0,4 μM respectively (or 1,1 and 0,1 $\mu\text{g/ml}$).

Plasma protein binding is relatively low (34 to 38 %) and so drug interactions involving

binding site displacement are not anticipated. In adults the average cerebrospinal fluid/plasma zidovudine concentration ratio 2 to 4 hours after chronic intermittent oral 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. In children over the age of five months, the pharmacokinetic profile of zidovudine is similar to that in adults. During continuous i.v. infusion in children, the mean steady-state cerebrospinal fluid/plasma concentration ratio was 0,24. 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.

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 (chromosome damage) 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).

PHARMACEUTICAL INFORMATION

List of Excipients:

Hydrochloric acid, sodium hydroxide, water for injection.

Shelf Life:

The expiry date is indicated on the packaging.

Storage:

Protect from light.

Keep out of reach of children.

Store at or below 30 °C.

Nature and Contents of Container:

Amber glass vial sealed with a rubber stopper and aluminium collar with plastic flip-top cover containing 20 ml.

PRESENTATION:

An amber glass vial containing 200 mg zidovudine in 20 ml.

Incompatibilities:

No data.

Use and Handling:

Dilution: RETROVIR IV must be diluted prior to administration. The required dose (see Dosage) should be added to and mixed with glucose i.v. infusion BP (5 % *m/v*) to give a final zidovudine concentration of either 2 mg or 4 mg/ml. These dilutions are chemically and physically stable for up to 48 hours at both 5 °C and 25 °C.

Since no antimicrobial preservative is included, dilution must be carried out under full

aseptic conditions, preferably immediately prior to administration, and any unused portion of the vial should be discarded. Should any visible turbidity appear in the product either before or after dilution or during infusion, the preparation should be discarded.

Not all presentations are available in every country.

Name and address of the applicant:

GlaxoSmithKline South Africa (Pty) Ltd

Flushing meadows Building

The Campus office park

57 Sloane Street,

Byranston, 2021

Name and address of the manufacturer:

Catalytica Pharmaceuticals Inc.

Greenville, North Caroliona, USA

Registration number:

Namibia: 04/20.2.8/0930 NS2

Version number: VGDS39/IP111

Date of issue: 06 August 2020

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