Revodine®
Zidovudine

FORMS AND PRESENTATION
Revodine®: Film coated tablets: Box of 60.
COMPOSITION
Revodine®: Each film coated tablet contains Zidovudine 300mg.
Excipients: microcrystalline cellulose, sodium starch glycolate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Therapeutic class: Antivirals for systemic use.
ATC code: J05AF01.
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 catalyzed 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.
Pharmacokinetic properties
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 Zidovudine, 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 Liters/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 fetal 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 glucuronidated 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.
INDICATIONS
Revodine® oral formulations are indicated in anti-retroviral combination therapy for Human Immunodeficiency Virus (HIV) infected adults and children.
Revodine® chemoprophylaxis is indicated for use in HIV-positive pregnant women (over 14 weeks of gestation) for prevention of maternal-fetal HIV transmission and for primary prophylaxis of HIV infection in newborn infants.
CONTRAINDICATIONS
- Zidovudine oral formulations are contra-indicated in patients known to be hypersensitive to Zidovudine, or to any of the excipients.
- Zidovudine oral formulations should not be given to patients with abnormally low neutrophil counts (less than 0.75 x 10^9/liter) or abnormally low hemoglobin levels (less than 7.5 g/deciliter or 4.65 mmol/liter).
- Zidovudine is contra-indicated in new born infants with hyperbilirubinemia requiring treatment other than phototherapy, or with increased transaminase levels of over five times the upper limit of normal.
PRECAUTIONS
Zidovudine is not a cure for HIV infection or AIDS. Patients receiving Zidovudine 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.
- Hematological Adverse Reactions: Anemia (usually not observed before six weeks of Zidovudine 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 Zidovudine; 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.
Hematological 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 hemoglobin 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 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 anemia, dosage adjustments do not necessarily eliminate the need for transfusions.
- Lactic acidosis: Lactic acidosis usually associated with hepatomegaly and hepatic steatosis has been reported with the use of nucleoside analogues. 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 nucleoside analogues 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 nucleoside analogues 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 toxicity: Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse events reported are hematological disorders (anemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behavior). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.
- Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesized. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. 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.
- 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 carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.
Patients should be cautioned about the concomitant use of self-administered medications.
Patients should be advised that Zidovudine therapy has not been proven to prevent the transmission of HIV to others through sexual contact or contamination with blood.
- 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.
Ability to drive and use machines
There have been no studies to investigate the effect of Zidovudine on driving performance or the ability to operate machinery. 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 Zidovudine should be borne in mind when considering the patient's ability to drive or operate machinery.
PREGNANCY AND LACTATION
The use of Zidovudine 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-fetal transmission of HIV based on viral cultures in infants.
A decision to reduce the risk of maternal transmission of HIV should be based on the balance of potential benefits and potential risk. Pregnant women considering the use of Zidovudine during pregnancy for prevention of HIV transmission to their infants should be advised that transmission may still occur in some cases despite therapy.
The efficacy of Zidovudine to reduce the maternal-fetal transmission in women with previously prolonged treatment with Zidovudine or other antiretroviral agents or women infected with HIV strains with reduced sensitivity to Zidovudine is unknown.
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. The relevance of these findings to both infected and uninfected infants exposed to Zidovudine is unknown. However, pregnant women considering using Zidovudine during pregnancy should be made aware of these findings.

Given the limited data on the general use of Zidovudine in pregnancy, Zidovudine should only be used prior to the 14th week of gestation when the potential benefit to the mother and fetus outweigh the risks.

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

Health experts recommend that women infected with HIV do not breast feed their infants in order to avoid the transmission of HIV. 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. Therefore, since the drug and the virus pass into breast milk it is recommended that mothers taking Zidovudine do not breast feed their infants.

DRUG INTERACTIONS

- 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.
- Zidovudine in combination with stavudine is antagonistic in vitro. The concomitant use of stavudine with Zidovudine should be avoided.
- Probenecid increases the AUC of Zidovudine by 106% (range 100 to 170%). Patients receiving both drugs should be closely monitored for hematological toxicity.
- 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.
- 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.
- In a pharmacokinetic study co-administration of Zidovudine and atovaquone showed a decrease in Zidovudine clearance after oral dosing leading to a 35%±23% increase in plasma Zidovudine AUC. The mode of interaction is unknown and as higher concentrations of atovaquone can be achieved with atovaquone suspension it is possible that greater changes in the AUC values for Zidovudine might be induced when atovaquone is administered as a suspension. Given the limited data available the clinical significance of this is unknown.
- 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 valproic acid, fluconazole or methadone, patients should be monitored closely for potential toxicity of Zidovudine.
- Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive drugs (e.g. 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 hematological 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 co-trimoxazole, aerosolized pentamidine, pyrimethamine and acyclovir 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.

ADVERSE EFFECTS

The adverse reaction profile appears similar for adults and children. The most serious adverse reactions include anemia (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/mm3. Dosage reduction or cessation of therapy may become necessary.

The incidence of neutropenia was also increased in those patients whose neutrophil counts, hemoglobin levels and serum vitamin B_{12} levels were low at the start of Zidovudine therapy.

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

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 (greater than 10%), Common (1 - 10%), Uncommon (0.1-1%), Rare (0.01-0.1%) and Very rare (less than 0.01%).

- Blood and lymphatic system disorders: Anemia, neutropenia and leucopenia (common); pancytopenia with bone marrow hypoplasia, thrombocytopenia (uncommon); pure red cell aplasia (rare); aplastic anemia (very rare).
- Metabolism and nutrition disorders: Lactic acidosis in the absence of hypoxemia, anorexia (rare).
- Psychiatric disorders: Anxiety and depression (rare).
- Nervous system disorders: Headache (very common); dizziness (common); Convulsions, loss of mental acuity, insomnia, paresthesia, somnolence (rare).
- Cardiac disorders: Cardiomyopathy (rare).
- Respiratory, thoracic and mediastinal disorders: Dyspnea (uncommon); cough (uncommon)
- Gastrointestinal disorders: Nausea (very common); vomiting, diarrhea and abdominal pain (common); flatulence (uncommon); pancreatitis, oral mucosa pigmentation, taste disturbance and dyspepsia (rare).
- Hepatobiliary disorders: Raised blood levels of liver enzymes and bilirubin (common); liver disorders such as severe hepatomegaly with steatosis (rare).
- Skin and subcutaneous tissue disorders: Rash and pruritis (uncommon); urticaria, nail and skin pigmentation, and sweating (rare).
- Musculoskeletal and connective tissue disorders: Myalgia (common); myopathy (uncommon).
- Renal and urinary disorders: Urinary frequency (rare).
- Reproductive system and breast disorders: Gynecomastia (rare)
- General disorders and administration site disorders: Malaise (common); asthenia, fever, and generalized pain (uncommon); chest pain and influenza-like syndrome, chills (rare).

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 Zidovudine.

In a placebo-controlled trial, overall clinical adverse reactions and laboratory test abnormalities were similar for women in the Zidovudine and placebo groups. However, there was a trend for mild and moderate anemia to be seen more commonly prior to delivery in the Zidovudine treated women.

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

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues.

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia and hyperlactatemia.

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.

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.

DOSAGE AND ADMINISTRATION

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

Dosage in adults and adolescents weighing at least 30 kg

The usual recommended dose of Revodine® in combination with other anti-retroviral agents is 250 or 300 mg twice daily.

Dosage adjustments in patients with hematological adverse reactions

Substitution of Revodine® should be considered in patients whose hemoglobin level or neutrophil count fall to clinically significant levels. Other potential causes of anemia or neutropenia should be excluded. Revodine® dose reduction or interruption should be considered in the absence of alternative treatments.

Dosage in the elderly

Revodine® 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 hematological parameters, appropriate monitoring of patients before and during use of Revodine® 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 hemodialysis or peritoneal dialysis is 100 mg every 6 to 8 hrs (300-400 mg daily). Hematological parameters and clinical response may influence the need for subsequent dosage adjustment.

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 hematological adverse reactions (anemia, leucopenia, neutropenia) and reduce the dose and/or increase the interval between doses as appropriate.

OVERDOSAGE

No specific symptoms or signs have been identified following acute overdose with Zidovudine apart from those listed as undesirable effects such as fatigue, headache, vomiting, and occasional reports of hematological disturbances. Following a report where a patient took an unspecified quantity of Zidovudine with serum levels consistent with an overdose of greater than 17 g there were no short term clinical, biochemical or hematological sequela identified.

Patients should be observed closely for evidence of toxicity and given the necessary supportive therapy.

Hemodialysis and peritoneal dialysis appear to have a limited effect on elimination of Zidovudine but enhance the elimination of the glucuronide metabolite.

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

Date of Revision: May 2013.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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Manufactured by Hetero Labs Limited, India
Packed by **Benta** S.A.L., Lebanon