SOUTH AFRICAN PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ASPEN LAMZID (tablets)

COMPOSITION

Each ASPEN LAMZID tablet contains:

Zidovudine 300 mg

Lamivudine 150 mg

Excipients:

Colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose PH 102, sodium starch glycolate, purified talc.

Sugar free

CATEGORY AND CLASS

A 20.2.8: Antiviral agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Mechanism of Action

Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3'-hydroxy (-OH) group is replaced by an azido ($-N_3$) group. Within cells,

zidovudine is converted to the active metabolite, zidovudine 5'-triphosphate (AztTP), by the sequential action of the cellular enzymes. Zidovudine 5'-triphosphate inhibits the activity of the HIV reverse transcriptase both by competing for utilisation with the natural substrate, deoxythymidine 5'-triphosphate (dTTP), and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation and therefore, the viral DNA growth is terminated. Zidovudine has a 100 to 300 fold greater affinity for inhibiting HIV reverse transcriptase than it does for inhibiting human DNA polymerase.

Lamivudine is also a synthetic nucleoside analogue like zidovudine. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue.

Antiviral activity

Low concentrations of zidovudine (< 0,001 to 0,04 µg/ml) inhibit acute HIV-1 infection in human T-cell lines and peripheral blood lymphocytes. Zidovudine is less active in human monocyte-macrophages or quiescent cells but inhibits HIV replication in human brain macrophages. Lamivudine inhibits HIV-1 and HIV-2 replication in *in vitro* systems. HIV-1 strains resistant to both lamivudine and zidovudine have been isolated. The resistant isolates showed reduced susceptibility to the antiretroviral agent and genotypic analysis has shown that the resistance was due to specific mutations in the HIV-1 reverse transcriptase. Combination therapy with zidovudine plus lamivudine delayed the emergence of mutations conferring resistance to zidovudine. In some patients harbouring zidovudine-resistant virus, combination therapy with zidovudine plus lamivudine restored phenotypic sensitivity to zidovudine. The potential for

cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved.

Pharmacokinetic properties

Zidovudine

Adults: After oral dosing, zidovudine is well absorbed from the gastrointestinal tract with a bioavailability of 60 to 70 %. Administration with a high fat meal decreases both the rate and extent of absorption. Peak and trough plasma concentrations are 0,4 to 0,5 µg/ml and 0,1 µg/ml, respectively, in those receiving 100 mg every 4 hours.

The peak plasma concentrations (C_{max}) of 1,97 ± 0,49 µg/ml were attained with ASPEN LAMZID tablets, 0,81 ± 0,38 hrs (T_{max}) following administration to healthy volunteers under fasting conditions. Cerebrospinal fluid concentrations range widely but average approximately 53 % of those in plasma in adults. Concentrations in blood are similar to those in saliva but lower than those in the semen. The mean plasma half-life is approximately 0,9 to 1,5 hours following oral dosing. The volume of distribution is about 1,4 to 1,7 litres per kg and protein binding is relatively low (20 to 38 %). Zidovudine undergoes first-pass hepatic metabolism and is rapidly metabolised to its 5'-O-glucuronide metabolite which has a similar elimination half-life but lacks anti-HIV activity. Another metabolite, 3'-amino-3'-deoxythymidine, is present in plasma at low concentrations and may contribute to myelotoxicity. Following oral administration, urinary recovery of zidovudine and its glucuronide metabolite accounts for 14 % and 75 % of the dose, respectively, and the total urinary recovery ranged from 63 % to 95 %. Renal clearance involves both glomerular filtration and tubular secretion. The clearance of zidovudine is decreased in patients with uraemia. Two to three fold increases in plasma levels and $t_{½}$ of elimination occur in cirrhosis.

Pregnancy: The pharmacokinetics of zidovudine are similar to those of non-pregnant adults. Neonatal blood concentrations are essentially equal to maternal serum levels.

Lamivudine

Adults: Following oral administration, lamivudine is well absorbed from the gastrointestinal with a bioavailability of about 80 %. The peak plasma concentrations (C_{max}) of 1,49 ± 0,30 µg/ml were attained with ASPEN LAMZID tablets and 1,30 ± 0,51 hrs (T_{max}) following administration to healthy volunteers under fasting conditions. The apparent volume of distribution is about 1,3 l/kg. Metabolism of lamivudine is a minor route of elimination; the only known metabolite of lamivudine in man being the trans-sulfoxide metabolite. Approximately 70 % of the dose is excreted in the urine. The intracellular $t_{½}$ of lamivudine triphosphate is prolonged, averaging over 10 hours in peripheral blood lymphocytes.

The exposure, C_{max} and half-life are all increased and clearance is decreased with diminishing renal function.

INDICATIONS

ASPEN LAMZID is indicated for the treatment of HIV infection when a combination therapy with zidovudine and lamivudine is required.

CONTRAINDICATIONS

ASPEN LAMZID is contraindicated in patients with hypersensitivity to zidovudine, lamivudine or to any other component of the product. Zidovudine and lamivudine are also contraindicated in patients with abnormally low neutrophil counts/haemoglobin levels.

Paediatrics: The safety and effectiveness of lamivudine has not been established in paediatric patients below 12 years of age.

WARNINGS AND SPECIAL PRECAUTIONS

Patients receiving ASPEN LAMZID may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by medical practitioners experienced in the treatment of patients with associated HIV diseases.

Patients should be advised that ASPEN LAMZID has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

Appropriate precautions should continue to be employed.
Patients at risk of developing illness associated with immune suppression should be carefully monitored.

ASPEN LAMZID should be stopped immediately in patients who develop abdominal pain, nausea or vomiting or with abnormal biochemical test results until pancreatitis has been excluded.

ASPEN LAMZID should be administered under the supervision of a doctor with experience of treating patients with HIV infection or AIDS. An appropriate treatment procedure requires access to suitable facilities e.g. for performing haematological monitoring investigations, including determination of viral load, CD4+ lymphocytes and for provision of blood transfusions if necessary.

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. In patients with early HIV disease (where bone marrow reserve is generally good), haematological

adverse reactions are infrequent. Depending on the overall condition of the patient, blood tests may be performed less often.

Caution should be exercised when administering ASPEN LAMZID to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease. These patients should be followed closely. Lactic acidosis generally occurred after a few months treatment.
Patients should be cautioned about the concomitant use of self-administered medications (see INTERACTIONS).

At present there are no results from controlled clinical trials evaluating the effect of therapy with ASPEN LAMZID on the clinical progression of HIV infection, such as the incidence of opportunistic infections or survival. Patients receiving this combination may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close observation of medical practitioners experienced in the treatment of patients with HIV-associated diseases.

Caution should be exercised when ASPEN LAMZID is administered to patients with impaired renal or hepatic function. Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients receiving ASPEN LAMZID. These are expected to occur more frequently at higher dosages and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease.

Occurrences of lactic acidosis (in the absence of hypoxaemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis have been reported with the use of ASPEN LAMZID. Treatment with ASPEN LAMZID should be discontinued in the setting of

rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology. Benign digestive symptoms such as nausea, vomiting and abdominal pain, respiratory symptoms or neurological symptoms might be indicative of lactic acidosis development. Severe cases, sometimes with fatal outcomes, were associated with pancreatitis, liver failure/hepatic steatosis, renal failure and higher levels of serum lactate.

Pregnancy: See HUMAN REPRODUCTION

Lactation: See HUMAN REPRODUCTION

Geriatrics: ASPEN LAMZID has not been specifically investigated in geriatric patients. Elderly patients are more likely to have decreased renal function. Therefore, care should be taken in dose selection and it may be useful to monitor renal function.

INTERACTIONS

Zidovudine

Blood-dyscrasia causing medications/bone marrow depressants/nephrotoxic medicines: Concurrent use of these medications with ASPEN LAMZID may cause an additive or synergistic myelosuppression/nephrotoxicity.

Hepatic-glucuronidation-metabolised medications: Medicines metabolised by hepatic glucuronidation, such as paracetamol, aspirin, cimetidine and sulphonamides may compete with ASPEN LAMZID for metabolism and decrease the clearance of ASPEN LAMZID or the other medication; this could potentially increase the risk of toxicity of either ASPEN LAMZID or the other medication.

Phenytoin: Increased or decreased plasma levels of phenytoin have been observed on concomitant administration with ASPEN LAMZID. Caution should be observed and plasma

levels monitored when the two medicines are co-administered.

Non-steroidal anti-inflammatory agents (NSAIDs): There may be an increased risk of haemotoxicity (e.g. neutropenia) during concomitant use of ASPEN LAMZID and NSAIDs, including paracetamol.

Other nucleoside analogues: In vitro studies have shown that, when combined, ASPEN LAMZID may show antagonistic activity with other nucleoside analogues including ribavirin and stavudine.

Lamivudine

Administration of trimethoprim/sulphamethoxazole results in an increase in lamivudine exposure because of the inhibition of renal excretion of lamivudine by the trimethoprim component; the sulphamethoxazole component does not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary.

HUMAN REPRODUCTION

Pregnancy

Safety of ASPEN LAMZID for use in pregnancy has not been established.

Lactation

In general, HIV-infected women are advised not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected. Although it is not known if ASPEN LAMZID is excreted in human milk, there is the potential for adverse effects from lamivudine in nursing infants. Mothers should be instructed not to breastfeed if they are receiving lamivudine.

DOSAGE AND DIRECTIONS FOR USE

Adults

The recommended oral dose of ASPEN LAMZID for adults and adolescents (at least 12 years of age) is 1 tablet (containing lamivudine 150 mg and zidovudine 300 mg) twice daily.

Because it is a fixed dose combination, ASPEN LAMZID should not be prescribed for patients requiring dose adjustment.

SIDE EFFECTS

Zidovudine

The adverse event profile appears similar for adults and children. The most serious adverse reactions include anaemia (often requiring transfusions), neutropenia and leucopenia. These occurred more frequently at higher dosages (1 200 to 1 500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment). Dosage reduction or cessation of therapy may become necessary. The incidence of neutropenia was also increased in patients with pre-existing neutropenia or anaemia, those with low Vitamin B_{12} levels and those taking paracetamol concomitantly.

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

The following events have been reported in patients treated with ASPEN LAMZID. They may also occur as part of the underlying disease process or in association with other medicines used in the management of HIV disease. The relationship between these events and the use of ASPEN LAMZID is therefore difficult to evaluate, particularly in the medically complicated situations which characterise advanced HIV disease. A reduction in dose or suspension of ASPEN LAMZID therapy may be warranted in the management of these conditions:

Gastrointestinal tract: Nausea, vomiting, abdominal pain, dyspepsia, anorexia, diarrhoea, flatulence, oral mucosa pigmentation.

Haematological: Anaemia, neutropenia, leucopenia, thrombocytopenia, pancytopenia with marrow hyperplasia.

Liver/pancreas: Liver disorders such as severe hepatomegaly with steatosis, raised blood levels of liver enzymes and bilirubin, pancreatitis.

Metabolic/endocrine: Lactic acidosis in the absence of hypoxaemia.

Musculoskeletal: Myalgia, myopathy.

Neurological/psychiatry: Headache, dizziness, insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions, anxiety, depression.

Respiratory tract: Dyspnoea, cough.

Skin: Nail and skin pigmentation, rash, urticaria, pruritis, sweating.

Miscellaneous: Urinary frequency, fever, generalised pain, chills, chest pain, influenza-like syndrome, asthaenia, taste perversion, malaise, gynaecomastia.

Lamivudine

Adverse events have been reported during therapy for HIV disease with lamivudine in combination with zidovudine. With many it is unclear whether they are related to lamivudine or are as a result of the underlying disease process.

Adverse events which have been commonly reported are headache, fever, rash, malaise, fatigue, alopecia, nausea, diarrhoea, vomiting, abdominal pain or cramps, insomnia, cough, nasal symptoms and musculoskeletal pain.

Cases of pancreatitis and peripheral neuropathy have been reported less frequently.

Neutropenia, anaemia, thrombocytopenia, transient rises in liver enzymes (AST, ALT) and rises in serum amylase have occurred.

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

Isolated cases of hypersensitivity reactions, hair loss, exacerbation of peripheral neuropathy and paronychia have been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage with ASPEN LAMZID may manifest in any of the symptoms described under “SIDE EFFECTS”.

Recommended treatment consists of the following:

- Supportive therapy
- Close observation of the patient especially for evidence of neurotoxicity and bone marrow suppression.

Zidovudine is not removed from the body by peritoneal dialysis or haemodialysis in sufficient amounts to warrant the use of dialysis in an overdose situation.

Limited data are available on the consequences of ingestion of acute overdoses with lamivudine in humans. There is no specific antidote for lamivudine.

IDENTIFICATION

A white to off-white, slightly mottled, oval, biconvex tablet with bevelled edges and debossed with E57.

PRESENTATION

BLISTER PACKS (60 TABLETS): One strip of 10 tablets in clear plastic pockets containing one tablet in each pocket and sealed with printed aluminum foil. Blisters placed into an outer carton of printed cardboard along with a printed package insert.

XACTICS 1 000 ml JAR (500 TABLETS): Amber, pvc xactics jar with a silica gel sachet and sealed with a white screw cap. Jar containing 500 tablets.

Packs of 60 tablets packed in an HDPE bottle, with a CRC polypropylene cap and a dessicant disk.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep the blister in the carton until required for use.

Protect from moisture and light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

38/20.2.8/0112

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

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