Pharmacode position may change as per Supplier’s m/c requirement & additional small pharma code may appear on the front / back panel

APPROVED
By Corinda Gaigher at 10:41 am, Jun 29, 2018

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telanie , 15:29:03, 11/07/2018

LODIZ
P1518117

LODIZ
P1518117

NOVAGEN
PHARMA

PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

LODIZ (Tablet)

COMPOSITION:

Each film-coated tablet contains lamivudine 150 mg and zidovudine 300 mg.

Excipients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, Opadry 13B58802 IH White (hypromellose, titanium dioxide, polyethylene glycol 400, polysorbate 80). Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Lamivudine and zidovudine are selective inhibitors of human immunodeficiency virus HIV-1 and HIV-2. Lamivudine has been shown to be synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Both drugs are metabolised, sequentially by intracellular kinases to the 5’-triphosphate (TP). Lamivudine-TP and zidovudine-TP are substrates for and competitive inhibitors of HIV reverse transcriptase. However, their main antiviral activity is through incorporation of the mono-phosphate form into the viral DNA chain, resulting in chain termination. Lamivudine and zidovudine triphosphates show significantly less affinity for host cell DNA polymerases.

Individually, lamivudine and zidovudine therapy has resulted in HIV clinical isolates, which show reduced sensitivity *in vitro* to the nucleoside analogue to which they have been exposed. However *in vitro* studies also 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 lamivudine plus zidovudine delays the emergence of zidovudine resistance in antiretroviral naïve patients.

Pharmacokinetic properties:

Lamivudine and zidovudine are well absorbed from the gastrointestinal tract. The bioavailability of oral lamivudine in adults is normally between 80 to 85 % and for zidovudine 60 to 70 %. Absorption of lamivudine is delayed, but not reduced, by ingestion with food. Binding to plasma protein is reported to be less than 36 %. Because of first-pass metabolism, systemic bioavailability of zidovudine is approximately 65 %. Bioavailability in neonates up to 14 days old is approximately 89 %, and in neonates over 14 days, it decreases to approximately 61 %. Administration with a high-fat meal may decrease the rate and extent of absorption. Lamivudine and zidovudine penetrate the central nervous system and reach the cerebrospinal fluid (CSF). Metabolism of lamivudine is a minor route of elimination. Lamivudine is mainly cleared by renal excretion of unchanged drug. Interactions with lamivudine are low due to the small extent of hepatic metabolism (5 to 10 %) and low plasma binding. The 5’-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50 to 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.

Pharmacokinetics of the lamivudine and zidovudine combination when used in combination with other antiretroviral agents:

Zidovudine:

Pharmacokinetic/drug interaction studies indicate that there were no clinically significant alterations to zidovudine pharmacokinetics when given concomitantly with the following antiretroviral agents:

- Nucleoside reverse transcriptase inhibitors (NRTI’s): zalcitabine, didanosine and abacavir;
- Non-nucleoside reverse transcriptase inhibitors (NNRTI’s): nevirapine and efavirenz; and
- Protease inhibitors: indinavir sulphate, saquinavir mesylate, ritonavir, amprenavir and nelfinavir.

There is a known interaction between zidovudine and stavudine (d4T) (see “**INTERACTIONS**”).
The concomitant use of these two agents should be avoided.

Lamivudine:

Pharmacokinetic/drug interaction studies indicate that there were no clinically significant alterations to Lamivudine pharmacokinetics when given concomitantly with the following antiretroviral agents:

- Non-nucleoside reverse transcriptase inhibitors (NNRTI’s): efavirenz; and
- Protease inhibitors: indinavir sulphate, ritonavir and nelfinavir.

Pharmacokinetics of lamivudine and zidovudine combination when used in combination with other tuberculostatic agents:

Zidovudine:

Co-administration of zidovudine and rifampicin decreases the AUC of zidovudine by approximately 48 %; however the clinical significance of this is unknown.

Lamivudine:

Metabolism of lamivudine is a minor route of elimination. Lamivudine is mainly cleared by renal excretion of unchanged drug. The likelihood of metabolic drug interactions e.g. rifampicin with lamivudine is low due to the small extent of hepatic metabolism (5 to 10 %) and low plasma binding.

INDICATIONS:

LODIZ is indicated as part of antiretroviral combination therapy for the treatment of HIV infected adults and children over 12 years of age, with progressive immunodeficiency (CD4 Count ≤ 500 cells/mm³).

CONTRAINDICATIONS:

- Hypersensitivity to lamivudine, zidovudine or to any ingredient of the preparation.
- Patients with abnormally low neutrophil counts (< 0,75 x 10^9/l), or abnormally low haemoglobin levels (< 7,5 g/dl).
- Children below the age of 12 years. Insufficient data available.
- The combination of zidovudine with either ribavirin or stavudine is antagonistic *in vitro*. The concomitant use of either ribavirin or stavudine with **LODIZ** should be avoided.

WARNINGS and SPECIAL PRECAUTIONS:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination, in the treatment of HIV infection.

Haematological:

Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients with advanced symptomatic HIV disease receiving zidovudine, therefore haematological parameters should be carefully monitored (see “**CONTRAINDICATIONS**”) in patients receiving **LODIZ**. These haematological effects are not usually observed before four to six weeks therapy. It is generally recommended that blood tests be performed for patients with advanced symptomatic HIV disease, on at least a bi-weekly basis for the first three months of therapy and thereafter at least monthly.

In patients with early HIV disease haematological adverse reactions are infrequent. Blood tests may be performed less often, for example every one to three months depending on the overall condition of the patient. If haemoglobin levels are decreased by more than 25 % from baseline and falls in the neutrophil count of more than 50 % from baseline more frequent monitoring may be required.

If severe anaemia or myelo-suppression occurs during treatment with **LODIZ** or in patients with pre-existing bone marrow compromise e.g. haemoglobin < 9 g/dl (5,59 mmol/l) or neutrophil count < 1,0 x 10^9/l (see “**DOSAGE AND DIRECTIONS FOR USE**”), dosage adjustment of zidovudine may be required. As dosage adjustment of **LODIZ** is not possible separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the individual package leaflets of these drugs for dosage specifications.

Lactic acidosis / hyperlactataemia:

Use of **LODIZ** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Rare but potentially fatal incidences of lactic acidosis, in the absence of hypoxaemia, and severe hepatomegaly with steatosis in patients treated with zidovudine have been reported. It is not known whether these events are causally related to zidovudine, but they have been reported in HIV-positive patients without AIDS.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/l) and the serum bicarbonate and respond as follows:

- Lactate 2 to 5 mmol/l with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.
- Lactate 5 to 10 mmol/l with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism).
- Lactate > 10 mmol/l: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

Caution should be exercised when administering **LODIZ** to patients with known risk factors for liver disease.

Treatment with **LODIZ** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

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.

Like many nucleoside analogues lamivudine and zidovudine show activity in *in vitro* mammalian tests, but neither of these products is mutagenic in bacterial tests. Lamivudine has not shown any genotoxic activity in *in vitro* studies.

Higher numbers of chromosome breakages in peripheral blood lymphocytes from AIDS patients receiving zidovudine treatment have also been observed. The clinical implications of these findings are unclear.

Both lamivudine and zidovudine were shown to cross the placenta in reproductive animal studies, and have demonstrated evidence of causing an increase in early embryonic deaths in the rabbit (lamivudine), or rat and rabbit (zidovudine). Lamivudine was not teratogenic in animal studies. Zidovudine given to rats during organogenesis at maternally toxic doses, resulted in an increased incidence of malformations. Foetal abnormalities did not occur at lower doses.

With regards to fertility studies in male and female rats, neither zidovudine nor lamivudine have shown evidence of impairment. No data is available on their effect of this combination on human female fertility. Sperm count morphology or motility has not been affected in men as a result of the use of zidovudine.

A carcinogenic risk to humans can thus not be excluded, due to the animal carcinogenicity and mutagenicity data. Lamivudine did not show any carcinogenic potential, in long-term oral carcinogenicity studies in rats and mice. Treatment-related effects were limited to late-appearing vaginal neoplasms, in animals treated with zidovudine. The relevance of these tumours for humans is still unclear, and any theoretical risk of carcinogenicity should be balanced against the proven therapeutic benefit.

The relevance of these findings to both infected and uninfected infants exposed to zidovudine is unknown. However, pregnant women considering using **LODIZ** during pregnancy should be informed of these findings.

Pancreatitis:

Pancreatitis has been observed in some patients receiving **LODIZ**. A causal relationship between drug treatment and underlying HIV disease could not be established. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **LODIZ** 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 **LODIZ** is increased due to decreased clearance. The dose of **LODIZ** should therefore be adjusted (see “**DOSAGE AND DIRECTIONS FOR USE**”).

Liver disease:

Use of **LODIZ** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **LODIZ** 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 leaflets 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.

When administering **LODIZ** to any patient, particularly obese women with hepatomegaly, hepatitis or other known risk factor for liver disease, caution should be exercised. These patients should be followed closely while on therapy with **LODIZ**.

Patients with HIV and hepatitis B or C virus co-infection:

Patients with chronic hepatitis B or C and treated with antiretroviral 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 leaflets for these medicines.

Patients co-infected with HIV and HBV who discontinue **LODIZ** 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.

Discontinuation of **LODIZ** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome:

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination antiretroviral therapy (cART). Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS.

Autoimmune disorders (such as Graves’ disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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 **LODIZ** 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:

Patients should be advised that current antiretroviral therapy, including **LODIZ**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

In cases where dosage adjustment is necessary, it is recommended that separate preparations of lamivudine and zidovudine should be administered. In these special cases the physician should refer to the individual package leaflets for these drugs.

Concomitant use of self-administered medications should be discouraged during treatment with **LODIZ** and patients should be cautioned in this regard (see “**INTERACTIONS**”).

No studies have been performed to investigate the effect of lamivudine or zidovudine on driving performance or the ability to operate machinery. Further, from the pharmacology of the drugs, a detrimental effect on such activities cannot be predicted. When considering the patient’s ability to drive or operate machinery, the clinical status of the patient and the adverse event profile of lamivudine and zidovudine should be borne in mind.

INTERACTIONS:

Any interactions that have been identified with zidovudine and lamivudine individually may occur in **LODIZ**. Due to limited metabolism and plasma protein binding, and almost complete renal clearance, the likelihood of metabolic interactions with lamivudine is low. Similarly zidovudine has limited protein binding but is eliminated primarily by hepatic conjugation to an inactive glucuronidated metabolite.

The interactions listed below should not be considered exhaustive but are representative of the classes of drug when caution should be exercised.

Interactions relevant to lamivudine:

Possible interactions with other drugs administered concurrently with **LODIZ** should be investigated, particularly when the main route of elimination is active renal secretion especially via the cationic transport system e.g. trimethoprim. The nucleoside analogues (e.g. zidovudine, didanosine and zalcitabine) and other drugs (e.g. ranitidine, cimetidine) are eliminated partly by this mechanism and were shown not to interact with lamivudine.

Please refer to the Pharmacokinetic properties section for full details on the interaction of lamivudine with other antiretroviral agents.

In has been reported that administration of prophylactic doses of co-trimoxazole resulted in increased lamivudine concentrations. This can be attributed due to the trimethoprim component, as the sulphamethoxazole component did not interact. No dosage adjustment of lamivudine is necessary, unless the patient has renal impairment, (see “**DOSAGE AND DIRECTIONS FOR USE**”).

Patients should be monitored clinically, when concomitant administration with co-trimoxazole is warranted. High doses of co-trimoxazole in combination with **LODIZ** for the treatment of Pneumocystis carinii pneumonia (PCP) and toxoplasmosis should be avoided. The doses studied showed that lamivudine has no effect on the pharmacokinetics of co-trimoxazole.

Until further information is available, co-administration of lamivudine with intravenous ganciclovir or foscarnet is not recommended.

Interactions relevant to zidovudine:

Zidovudine has no effect on the pharmacokinetics of lamivudine. A slight increase in C_{max} (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly changed.

The co-administration of zidovudine and rifampicin decreases the AUC of zidovudine by 48 % ± 34 %. However, the clinical significance of this is unknown.

In some patients receiving zidovudine, the phenytoin blood levels have been reported to be low, while in one patient a high level was noted. These observations imply that phenytoin concentrations should be monitored carefully in patients receiving **LODIZ** in combination with phenytoin.

Paracetamol use during treatment with zidovudine in a placebo-controlled trial was associated with an increased incidence of neutropenia especially following chronic therapy. However, the available pharmacokinetic data indicate that paracetamol at the doses studied does not increase plasma levels of zidovudine nor of its glucuronide metabolite.

The following drugs, including but not limited to, may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism: aspirin, codeine, morphine, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and isoprinosine. The possibilities of drug interaction before using such drugs, particularly for chronic therapy, in combination with **LODIZ**, should be considered.

The risk of adverse reactions to zidovudine may also increase with concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelo-suppressive drugs (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin). 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, if concomitant therapy with **LODIZ** and any of these drugs is necessary.

The combination of zidovudine with either ribavirin or stavudine is antagonistic *in vitro*. The concomitant use of either ribavirin or stavudine with **LODIZ** should be avoided, (see “**CONTRAINDICATIONS**”).

The concomitant use of prophylactic antimicrobial therapy may have to be considered, since some patients receiving **LODIZ** may continue to experience opportunistic infections. This named prophylaxis has included pyrimethamine, co-trimoxazole, aerosolised pentamidine and acyclovir. The limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with these drugs.

By decreasing glucuronidation, limited data suggested that probenecid increased the mean half-life and area under the plasma concentration curve of zidovudine. In the presence of probenecid, renal excretion of the glucuronide (and possibly zidovudine itself) is reduced.

HUMAN REPRODUCTION:

Pregnancy:

The safety of lamivudine in human pregnancy has not been established thus treatment during the first trimester of pregnancy is not advised.

The use of zidovudine in pregnant women, with subsequent treatment of the new-born infants, has been shown to reduce the rate of maternal-foetal transmission of HIV. This has however not been established for lamivudine. Consequently the administration of **LODIZ** during pregnancy should only be considered if expected benefits outweigh any possible risks.

Lactation:

Studies in lactating rats showed that, following oral administration, lamivudine and zidovudine were excreted in the milk. It is not known if lamivudine or zidovudine is excreted in human milk. Since these drugs may pass into breast milk, it is recommended that mothers taking **LODIZ** do not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE:

Adults and children over the age of 12 years:

The recommended dose: one tablet twice daily.

LODIZ may be administered with or without food.

A physician experienced in the management of HIV infection should initiate therapy. During combination therapy with other antiretroviral agents, the package leaflet of the particular agent should be consulted for information.

Renal impairment:

Due to decreased clearance in patients with renal impairment, the concentrations of lamivudine and zidovudine are elevated. Therefore as dosage adjustment of these may be required, it is advised that separate preparations of lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance ≤ 50 ml/min). The package leaflet for separate preparations must be consulted for full details of these dosage adjustments.

Hepatic impairment:

The influence of hepatic impairment on lamivudine levels has not been fully elucidated. Lamivudine clearance is largely renal. Based on preliminary safety data no dosage adjustment is necessary. Lamivudine should be used with caution in patients with hepatomegaly or other risk factors for hepatic disease. Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Therefore as dosage adjustments for zidovudine may be necessary, it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with severe hepatic impairment. The package leaflet of zidovudine must be consulted for full details of the dosage adjustments.

Dosage adjustments in patients with haematological adverse reactions:

Dosage adjustment of zidovudine may be necessary if the haemoglobin level falls below 9 g/dl or 5,59 mmol/l or the neutrophil count falls below 1,0 x 10^9/l (see “**CONTRAINDICATIONS**”). This is more likely in patients with poor bone marrow reserve prior to treatment, particularly in patients with advanced HIV disease. As dosage adjustment is not possible for **LODIZ,** separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the individual package leaflet for these drugs.

Dosage in the elderly:

Special care is advised in geriatric patients due to age-associated changes such as the decrease in renal function and alteration of haematological parameters.

SIDE EFFECTS:

During therapy for HIV disease with lamivudine and zidovudine separately or in combination, adverse events have been reported. With many of these events it is unclear whether they are related to lamivudine, zidovudine or to the wide range of drugs used in the management of HIV disease or are as a result of the underlying disease process.

As **LODIZ** contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of synergistic toxicity following concomitant administration of the two compounds.

Lamivudine: The adverse events, which have been reported, are:

Nervous system disorders:

Frequent: Headache, insomnia.

Less frequent: Although no relationship to the dose of lamivudine has been reported, cases of peripheral neuropathy (or paraesthesia) have been recorded.

Musculoskeletal, connective tissue and bone disorders:

The following side effects have been reported but the frequencies are unknown: Malaise, fatigue, musculoskeletal pain.

Gastrointestinal disorders:

Frequent: Nausea, diarrhoea, vomiting, abdominal pain or cramps.

Respiratory, thoracic and mediastinal disorders:

The following side effects have been reported but the frequencies are unknown: Cough, nasal symptoms.

Endocrine disorders:

The following side effects have been reported but the frequencies are unknown: Although no relationship to the dose of lamivudine has been reported, cases of pancreatitis have been recorded.

Blood and the lymphatic system disorders:

Frequent: Anaemia and neutropenia (both occasionally acute) have occurred in combination with zidovudine.

Thrombocytopenia has been reported.

Investigations:

The following side effects have been reported but the frequencies are unknown: Transient rises in liver enzymes (AST, ALT) and rises in serum amylase have been reported.

Zidovudine:

Blood and the lymphatic system disorders:

Anaemia (which may require transfusions), neutropenia and leucopenia, have been reported as the most serious adverse reactions. These adverse reactions occur more often at higher dosages (1 200 to 1 500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4 cell counts < 100/mm³. A reduction in the dosage or cessation of therapy may become essential (see “**DOSAGE AND DIRECTIONS FOR USE**”).

Adverse events have been reported in patients whose neutrophil counts, haemoglobin levels and serum vitamin B_{12} levels were low at the start of zidovudine therapy, and in those patients who are concurrently taking paracetamol (see “**INTERACTIONS**”).

Gastrointestinal disorders:

Frequent: Nausea, vomiting, anorexia, abdominal pain, dyspepsia.

Nervous system disorders:

Frequent: Headache, paraesthesia, asthenia, insomnia.

Skin and subcutaneous tissue disorders:

Frequent: Rash.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia, malaise.

Nausea was considerably more common in all studies in patients receiving zidovudine, the other adverse events were not consistently reported to be more frequent in occurrence than in the placebo recipients. Vomiting, anorexia, malaise and asthenia were more common in zidovudine-treated patients with early HIV disease, whilst severe headache, myalgia and insomnia were more common in zidovudine-treated patients with advanced HIV disease.

General disorders and administration site conditions:

Frequent: Fever.

The following side effects have been reported but the frequencies are unknown: Somnolence, diarrhoea, dizziness, sweating, dyspnoea, flatulence, taste perversion, pain in the chest, loss of mental acuity, anxiety, urinary frequency, depression, generalised pain, chills, cough, urticaria, pruritus and an influenza-like syndrome, have been recorded as other adverse events associated with the use of **LODIZ**.

The occurrence of these and other less frequent adverse events was similar in both zidovudine and placebo-treated patients. The incidence of nausea and other frequently reported clinical adverse events consistently decrease over time during the first few weeks of therapy with zidovudine, this was indicated by available data from both placebo-controlled and open-labelled studies.

The relationship between the following events, which have been reported on, and the use of zidovudine is difficult to evaluate, if the medically complicated situations, which characterise advanced HIV disease is considered (see **“WARNINGS and SPECIAL PRECAUTIONS**”):

Hepato-biliary disorders:

The following side effects have been reported but the frequencies are unknown: Lactic acidosis in the absence of hypoxaemia, liver disorders such as severe hepatomegaly with steatosis.

Musculoskeletal, connective tissue and bone disorders:

The following side effects have been reported but the frequencies are unknown: Myopathy.

Blood and the lymphatic system disorders:

The following side effects have been reported but the frequencies are unknown: Pancytopenia with marrow hypoplasia and isolated thrombocytopenia.

Investigations:

The following side effects have been reported but the frequencies are unknown: Raised blood levels of liver enzymes and bilirubin.

Endocrine disorders:

The following side effects have been reported but the frequencies are unknown: Pancreatitis.

Musculoskeletal, connective tissue and bone disorders:

The following side effects have been reported but the frequencies are unknown: Nail, skin and oral mucosa pigmentation.

Nervous system disorders:

The following side effects have been reported but the frequencies are unknown: In patients receiving open-label therapy with zidovudine, convulsions and other cerebral events have also been recorded. The beneficial effect of zidovudine on HIV-associated neurological disorders, has overall been proven by the weight of evidence.

A reduction or suspension of zidovudine therapy may assist in the assessment and management of these conditions. If the severity of the symptoms warrants it, **LODIZ** should be discontinued and separate preparations of zidovudine and lamivudine should be administered, if symptoms become intolerable (see “**WARNINGS and SPECIAL PRECAUTIONS**”).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no experience of overdosage with **LODIZ**. Limited data is available on the consequences of ingestion of acute overdoses of lamivudine and zidovudine in humans. All patients recovered, no fatalities occurred.

Following such overdosage, no specific signs or symptoms have been identified.

Treatment of overdosage:

In the event of an overdosage the patient should be monitored for evidence of toxicity (see “**SIDE EFFECTS**” and “**WARNINGS and SPECIAL PRECAUTIONS**”), and standard supportive treatment be applied as necessary. Continuous haemodialysis could be used in the treatment of overdosage, since lamivudine is dialysable, although this has not been studied.

Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine, but enhance the elimination of the glucuronide metabolite. Physicians should refer to the individual package leaflets for lamivudine and zidovudine, for more details. Patients, in whom intentional overdose is confirmed or suspected, should be referred for psychiatric consultation.

IDENTIFICATION:

White modified capsule shaped, biconvex, film-coated tablets, debossed with ‘C’ and ‘60’ on one side and plain on the other side.

PRESENTATION:

1. 60 tablets are packed in a white 110 ml HDPE container (heavy weight) closed with a cap containing induction sealing wad.
2. 60 tablets are packed in white round 75 ml HDPE container (heavy weight) with stock ribbed polypropylene closure with induction sealing wad.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Protect from light and moisture.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

A40/20.2.8/0381

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

Novagen Pharma (Pty) Ltd
Office 2, 100 Sovereign Drive
Route 21 Corporate Park
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South Africa

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

Date of registration: 11 August 2006
Date of latest revision of the text as approved by Council: 11 August 2006
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↑DETACH BEFORE DISPENSING

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

LODIZ (Tablet)

Lamivudine / Zidovudine.

Read all of this leaflet carefully before you start taking LODIZ

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **LODIZ** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. WHAT LODIZ CONTAINS

- The active substances are lamivudine and zidovudine. Each film-coated tablet contains lamivudine 150 mg and zidovudine 300 mg.
- The other ingredients are: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, Opadry 13B58802 IH White (hypromellose, titanium dioxide, polyethylene glycol 400, polysorbate 80).
- Sugar free.

2. WHAT LODIZ IS USED FOR

LODIZ tablets are indicated as part of an antiretroviral combination therapy for the treatment of HIV infected adults and children over 12 years of age, with progressive immunodeficiency (CD4 Count ≤ 500 cells/mm³).

3. BEFORE YOU TAKE LODIZ

Do not take LODIZ:

- If you are hypersensitive (allergic) to lamivudine or zidovudine or any of the other ingredients of **LODIZ** tablets.
- Not recommended for use in children below 12 years of age. Insufficient data available.
- If you have abnormally low neutrophil counts (<0,75 x 10^9/l), or abnormally low haemoglobin levels (<7,5 g/dl).
- The combination of zidovudine with either ribavirin or stavudine is antagonistic *in vitro*. The concomitant use of either ribavirin or stavudine with **LODIZ** should be avoided.

Take special care with LODIZ:

- You may develop a potentially fatal condition known as lactic acidosis while taking **LODIZ**. Inform your doctor or other healthcare professional immediately if you develop nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Your doctor will perform blood tests and treat you accordingly.
- If you became pregnant while taking **LODIZ** your baby may develop blood and nervous system disorders. Your doctor will monitor your baby’s condition.
- Pancreatitis (inflammation of the pancreas) has been observed in some patients receiving **LODIZ**. Inform your doctor or other healthcare professional immediately if you develop abdominal pain, nausea or vomiting. Your doctor will discontinue treatment with **LODIZ** until the diagnosis of pancreatitis is excluded.
- If you have kidney problems your doctor or healthcare professional will need to adjust the dosage of **LODIZ**.
- You may develop liver problems when taking **LODIZ**. Inform your doctor or healthcare professional if you have any pre-existing liver disease including Hepatitis B or C.

Do not stop taking **LODIZ** if you are co-infected with HIV and Hepatitis as this may cause the Hepatitis to worsen.

- You may develop a condition known as lipodystrophy while taking **LODIZ**. Inform your doctor or healthcare professional if you notice a change in the distribution of your body fat (e.g. accumulation of fat around the waist/stomach area, on the back of the neck and between the shoulders (buffalo hump), breast enlargement), wasting of the arms, legs and facial muscles, and increased blood glucose and lipid values.
- If you are taking **LODIZ** for the first time you may develop a condition known as Immune Reconstitution Inflammatory Syndrome (IRIS), within the first few months of treatment. This condition can cause opportunistic infections that are being treated to become worse or opportunistic diseases that were asymptomatic to be unmasked. Tell your doctor or healthcare professional if your general health worsens or if you think you may have an infection. You should not stop taking **LODIZ**, Your doctor will treat the infections appropriately.
- You may develop a condition known as osteonecrosis while taking **LODIZ**. Seek medical advice if you experience joint aches and pain, joint stiffness or difficulty in movement.
- You may continue to develop opportunistic infections and other complications of HIV infection while taking **LODIZ**. You 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.
- You are still at risk of transmitting HIV to others through sexual contact or blood contamination while taking current antiretroviral therapy including **LODIZ**. Appropriate precautions should continue to be employed.

Taking LODIZ with food and drink:

LODIZ tablets can be taken with or without food.

Pregnancy and Breastfeeding:

The safety of lamivudine in human pregnancy has not been established thus treatment during the first trimester of pregnancy is not advised.

The use of zidovudine in pregnant women, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal-foetal transmission of HIV. This has however not been established for lamivudine. Consequently the administration of **LODIZ** during pregnancy will only be considered if expected benefits outweigh any possible risks.

Studies in lactating rats showed that, following oral administration, lamivudine and zidovudine were excreted in the milk. It is not known if lamivudine or zidovudine are excreted in human milk. Since these drugs may pass into breast milk, it is recommended that mothers taking **LODIZ** do not breastfeed their infants.

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking **LODIZ**.

Taking other medicines with LODIZ:

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines).

LODIZ interacts with trimethoprim.

Prophylactic use of co-trimoxazole may increase the concentration of the lamivudine in the blood. The dose may need to be adjusted if the doctor confirms that you may have renal impairment.

The doctor will monitor the blood levels of phenytoin, if you are taking this drug.

Aspirin, codeine, morphine, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and isoprinosine may interfere with the metabolism of zidovudine. The doctor will monitor any significant effect, if you are currently taking any of these drugs with **LODIZ.** If you are currently on systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine or vinblastine, the risk of increasing the adverse effects of zidovudine may be potentially serious. The doctor will monitor your renal and haematological parameters and consider if any dosage adjustments may be necessary.

4. HOW TO TAKE LODIZ

Do not share medicines prescribed for you with any other person.

Always take **LODIZ** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of **LODIZ** is too strong or too weak, talk to your doctor or pharmacist.

Adults and children over the age of 12 years:

- The recommended dose: one tablet orally twice daily.
- The therapy should be initiated by a doctor experienced in the management of HIV infection. **LODIZ** tablets can be taken with or without food.
- Dosage adjustments may be deemed necessary if your doctor confirms that you have renal and hepatic impairment or any increased risk of haematological adverse reactions.

If you take more LODIZ than you should:

If overdosage occurs the patient should be monitored and standard supportive treatment supplied as required.
In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take LODIZ:

Do not take a double dose to make up for forgotten individual doses.

5. POSSIBLE SIDE EFFECTS

LODIZ can have side effects.

LODIZ is a combination of both lamivudine and zidovudine and hence each of these drugs can cause side effects.

Lamivudine: The adverse events, which have been reported, are:

Nervous system disorders:

Frequent: Headache, insomnia.

Less frequent: Although no relationship to the dose of lamivudine has been reported, cases of peripheral neuropathy (or paraesthesia) have been recorded.

Musculoskeletal, connective tissue and bone disorders:

The following side effects have been reported but the frequencies are unknown: Malaise, fatigue, musculoskeletal pain.

Gastrointestinal disorders:

Frequent: Nausea, diarrhoea, vomiting, abdominal pain or cramps.

Respiratory, thoracic and mediastinal disorders :

The following side effects have been reported but the frequencies are unknown: Cough, nasal symptoms

Endocrine disorders:

The following side effects have been reported but the frequencies are unknown: Although no relationship to the dose of lamivudine has been reported, cases of pancreatitis have been recorded.

Blood and the lymphatic system disorders:

Frequent: Anaemia and neutropenia (both occasionally acute) have occurred in combination with zidovudine. Thrombocytopenia has been reported.

Investigations:

The following side effects *have been reported but the frequencies are unknown:* Transient rises in liver enzymes (AST, ALT) and rises in serum amylase have been reported.

Zidovudine: The adverse events, which have been reported, are:

Blood and the lymphatic system disorders:

Anaemia (which may require transfusions), neutropenia and leucopenia, have been reported as the most serious adverse reactions. These adverse reactions occur more often at higher dosages (1 200 to 1 500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment) and particularly in patient with CD4 cell counts < 100 mm³, reduction in the dosage or cessation of therapy may become essential.

Adverse events have been reported, in patients whose neutrophil counts haemoglobin levels and serum, vitamin B_{12} levels were low at the start of zidovudine therapy, and in those patients who are concurrently, taking paracetamol.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, anorexia, abdominal pain, dyspepsia.

Nervous system disorders:

Frequent: Headache, paraesthesia, asthenia, insomnia.

Skin and subcutaneous tissue disorders:

Frequent: Rash.

Musculoskeletal. connective tissue and bone disorders:

Frequent: Myalgia, malaise.

Nausea was considerably more common in all studies in patients receiving zidovudine, the other adverse events were not consistently reported to be more frequent in occurrence than in the placebo recipients.

Vomiting, anorexia, malaise and asthenia were more common in zidovudine-treated patients with early HIV disease, whilst severe headache, myalgia and insomnia were more common in zidovudine treated patients with advanced HIV disease.

General disorders and administration site conditions:

Frequent: Fever.

The following side effects have *been reported but the frequencies* are *unknown:* Somnolence, diarrhoea, dizziness, sweating, dyspnoea, flatulence, taste perversion, pain in the chest, loss of mental acuity, anxiety, urinary frequency, depression, generalised pain, chills, cough, urticaria, pruritus and influenza-like syndromes, have been recorded as other adverse events associated with the use of **LODIZ**.

The occurrence of these and other less frequent adverse events was similar in both zidovudine and placebo-treated patients. The incidence of nausea and other frequently reported clinical adverse events consistently decrease over time during the first few weeks of therapy with zidovudine, this was indicated by available data from both placebo-controlled and open-labelled studies.

The relationship between the following events, which have been reported on, and the use of zidovudine is difficult to evaluate, if the medically complicated situations, which characterise advanced HIV disease is considered.

Hepato-biliary disorders:

The following side effects have been reported but the frequencies are unknown: Lactic acidosis in the absence of hypoxaemia, liver disorders such as severe hepatomegaly with steatosis.

Musculoskeletal, connective tissue and bone disorders:

The following side effects have been reported but the frequencies are unknown: Myopathy.

Blood and the lymphatic system disorders:

The following side effects *have been reported but the frequencies* are *unknown:* Pancytopenia with marrow hypoplasia and isolated thrombocytopenia.

Investigations:

The following side effects have been reported but the frequencies are unknown: Raised blood levels of liver enzymes and bilirubin.

Endocrine disorders:

The following side effects have been reported but the frequencies are unknown: Pancreatitis.

Musculoskeletal, connective tissue and bone disorders:

The following side effects have been reported but the frequencies are unknown: Nail, skin and oral mucosa pigmentation.

Nervous system disorders:

The following side effects have been reported but the frequencies are unknown: In patients receiving open-label therapy with zidovudine, convulsions and other cerebral events have also been recorded. The beneficial effect of zidovudine on HIV-associated neurological disorders has overall been proven by the weight of evidence.

A reduction or suspension of zidovudine therapy may assist in the assessment and management of these conditions. If the severity of the symptoms warrants it, **LODIZ** should be discontinued and separate preparations of zidovudine and lamivudine should be administered, if symptoms become intolerable.

Not all side effects reported for **LODIZ** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **LODIZ**, please consult your doctor, pharmacist or other healthcare professional for advice.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING AND DISPOSING OF LODIZ

Store at or below 30 °C. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. PRESENTATION OF LODIZ

1. 60 tablets are packed in a white 110 ml HDPE container (heavy weight) closed with a cap containing induction sealing wad.
2. 60 tablets are packed in white round 75 ml HDPE container (heavy weight) with stock ribbed polypropylene closure with induction sealing wad.

Not all packs and pack sizes are necessarily marketed.

8. IDENTIFICATION OF LODIZ

White modified capsule shaped, biconvex, film-coated tablets, debossed with ‘C’ and ‘60’ on one side and plain on the other side.

9. REGISTRATION NUMBER

A40/20.2.8/0381

10. NAME, BUSINESS ADDRESS AND TELEPHONE NUMBER OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd

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11. DATE OF PUBLICATION OF THE PATIENT INFORMATION LEAFLET

Date of registration: 11 August 2006

Date of latest revision of the text as approved by Council: 11 August 2006

Date of notification with regard to amended Reg. 9 and 10: 02 February 2015

Black A/s: 350 x 720 mm

AUROBINDO Packaging Development	Product Name: Lodiz	Component: Leaflet	Item Code: P1518117	Date & Time: 27.06.2018 & 5.30 PM
	Customer / Country: ARV’s_SA	Version No.: 03	Reason Of Issue: Revision	Reviewed / Approved by
Team Leader: Kiran Kumar	Dimensions: 350 x 720 mm	No. of Colours : 01		
Initiator: Bhogeshwar				
Artist: Vision Graphic Designers	Pharmacode: 18117			Sign / Date
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PROFESSIONELE INLIGTING:

SKEDULERINGSTATUS:

S4

NOVAGEN PHARMA

EIENDOMSNAAM EN DOSEERVORM:

LODIZ (Tablet)

SAMESTELLING:

Elke filmbedekte tablet bevat 150 mg lamivudien en 300 mg sidovudien.

Eksipiënte: kolloïdale silikoondioksied, magnesiumstearaat, mikrokristallyne sellulose, natriumstyselglikolaat, Opadry 13B58802 IH Wit (hipromellose, titaandioksied, poliëtileenglikol 400, polisorbaat 80).

Suikervry.

FARMAKOLOGIESE KLASSIFIKASIE:

A 20.2.8 Virusteenmiddels

FARMAKOLOGIESE WERKING:

Farmakodinamiese eienskappe:

Lamivudien en sidovudien is selektiewe inhibeerders van menslike immuuntekortvirus MIV-1 en MIV-2.

Dit is aangetoon dat lamivudien sinergisties met sidovudien in die inhibisie van replisering van MIV in selkultuur is. Beide middels word opeenvolgend deur sellulêre kinases na die 5'-trifosfaat (TF) gemetaboliseer. Lamivudien- TF en sidovudien-TF is substrate vir en inhibeerders van MIV-trutranskriptase. Hul belangrikste antivirusaktiwiteit is egter deur die inkorporering van die monofosfaatvorm in die virus DNA-ketting, wat lei tot die beëindiging van die ketting. Lamivudien- en sidovudien- trifosfaat toon aansienlik minder affiniteit vir DNA-polimerases van die gasheersel.

Individueel het lamivudien- en sidovudienterapie tot MIV-kliniese isolate, wat *in vitro* 'n verlaagde sensitiwiteit tot die nukleosiedanaloog waaraan hulle blootgestel is toon, gelei. *In vitro* studies toon egter ook aan dat sidovudien-weerstandbiedende virusisolate sidovudiensensitief raak wanneer hulle terselfdertyd weerstandbiedend teen lamivudien raak. *In vivo* is daar verder kliniese bewys dat lamivudien plus sidovudien die ontwikkeling van sidovudienweerstand by pasiënte wat naïef tot antiretrovirusmiddels is, vertraag.

Farmakokinetiese eienskappe:

Lamivudien en sidovudien word goed vanuit die maagdermkanaal geabsorbeer. Die biobeskikbaarheid van orale lamivudien by volwassenes is normaalweg tussen 80 tot 85 % en vir sidovudien 60 tot 70 %. Die absorpsie van lamivudien word deur die inname van voedsel vertraag, maar nie verminder nie. Daar word aangemeld dat die binding aan plasmaproteïen minder as 36 % is.

Weens eerstedeurgang metabolisme is die sistemiese biobeskikbaarheid van sidovudien ongeveer 65 %. Die biobeskikbaarheid by neonate tot op 14 dae ouderdom is 89 %. By neonate ouer as 14 dae neem dit af na ongeveer 61 %. Toediening saam met 'n hoë-vet maaltyd kan die tempo en mate van absorpsie vertraag.

Lamivudien en sidovudien penetreer die sentrale senuweestelsel en bereik die serebrospinale vloeistof (SSV).

Die metabolisme van lamivudien is 'n minder belangrike roete van eliminasie. Lamivudien word hoofsaaklik as onveranderde middel deur die niere uitgeskei. Interaksies met lamivudien is min weens die geringe mate van lewermetabolisme (5 tot 10 %) en lae plasmabinding daarvan.

Die 5'-glukuronied van sidovudien is die belangrikste metaboliet in beide die plasma en urien en verteenwoordig ongeveer 50 tot 80 % van die toegediende dosis wat deur die niere uitgeskei word. 3'-amino 3'-deoksitimidien (AMT) is as 'n metaboliet van sidovudien na intraveneuse toediening geïdentifiseer.

Farmakokinetika van die lamivudien- en sidovudienkombinasie wanneer in kombinasie met ander antiretrovirusmiddels gebruik word:

Sidovudien:

Farmakokinetiese en middelinteraksiestudies toon aan dat daar geen klinies betekenisvolle veranderinge in die farmakokinetika van sidovudien was wanneer dit saam met die volgende antiretrovirusmiddels toegedien is nie:

- Nukleosied trutranskriptaseïnhibeerders (NTTIs): salsitabien, didanosien en abasavir;
- Nie-nukleosied trutranskriptaseïnhibeerders (NNTTIs): nevirapien en efavirens; en
- Proteaseïnhibeerders: indinavirsulfaat, sakinavirmesilaat, ritonavir, amprenavir en nelfinavir.

Daar is 'n bekende interaksie tussen sidovudien en stavudien (d4T) (sien "**INTERAKSIES**"). Die gelyktydige gebruik van hierdie middels behoort vermy te word.

Lamivudien:

Farmakokinetiese en middelinteraksiestudies toon aan dat daar geen klinies betekenisvolle veranderinge in die farmakokinetika van lamivudien was wanneer dit saam met die volgende antiretrovirusmiddels toegedien is nie:

- Nie-nukleosied trutranskriptaseïnhibeerders (NNTTIs): efavirens; en
- Proteaseïnhibeerders: indinavirsulfaat, ritonavir en nelfinavir.

Farmakokinetika van die lamivudien- en sidovudienkombinasie wanneer in kombinasie met ander tuberkulostatiese middels gebruik word:

Sidovudien:

Die medetoediening van sidovudien en rifampisien verminder die AOK van sidovudien met ongeveer 48 %. Die kliniese betekenis hiervan is egter onbekend.

Lamivudien:

Die metabolisme van lamivudien is 'n minder belangrike roete van eliminasie. Lamivudien word hoofsaaklik as onveranderde middel deur die niere uitgeskei. Die waarskynlikheid van middelinteraksies bv. rifampisien met lamivudien is klein weens die geringe lewermetabolisme (5 tot 10 %) en lae plasmabinding daarvan.

INDIKASIES:

LODIZ word aangedui as deel van antiretrovirus kombinasieterapie vir die behandeling van MIV-geïnfekteerde volwassenes en kinders ouer as 12 jaar, met progressiewe immuuntekort (CD4 waarde ≤ 500 selle/mm³).

KONTRA-INDIKASIES:

- Hipersensitiwiteit teen lamivudien, sidovudien of enige bestanddeel van die preparaat.
- Pasiënte met abnormaal lae neutrofieltellings (< 0,75 x 10^9/l), of abnormaal lae hemoglobienvlakke (< 7,5 g/dl).
- Kinders jonger as 12 jaar oud. Onvoldoende data beskikbaar.
- *In vitro* is die kombinasie van sidovudien met óf ribavirien óf stavudien antagonisties. Die gelyktydige gebruik van óf ribavirien óf stavudien saam met **LODIZ** behoort vermy te word.

WAARSKUWINGS en SPESIALE VOORSORGMAATREËLS:

Melksuurasidose en erge hepatomegalie met steatose, insluitend fatale gevalle, is met die gebruik van lamivudien alleen of in kombinasie, by die behandeling van MIV-infeksie aangemeld.

Hematologies:

Daar kan verwag word dat bloedarmoede, neutropenie en leukopenie (gewoonlik sekondêr tot neutropenie) voorkom by pasiënte met gevorderde simptomatiese MIV-siekte wat sidovudien ontvang. Daarom moet hematologiese parameters noukeurig gemoniteer word (sien **"KONTRA-INDIKASIES"**) by pasiënte wat **LODIZ** ontvang. Hierdie hematologiese effekte word gewoonlik nie voor 4 tot 6 weke van terapie waargeneem nie. Daar word gewoonlik aanbeveel dat bloedtoetse uitgevoer word vir pasiënte met gevorderde simptomatiese MIV-siekte, ten minste op 'n twee-weeklikse basis vir die eerste drie maande van terapie en daarna minstens maandeliks.

By pasiënte met vroeë MIV-siekte kom hematologiese newe-effekte nie dikwels voor nie. Bloedtoetse kan minder gereeld uitgevoer word, byvoorbeeld elke een tot drie maande, afhangende van die algehele toestand van die pasiënt. Indien hemoglobienvlakke met meer as 25 % van die basislyn en die neutrofiele telling met meer as 50 % van die basislyn afneem, kan meer monitering vereis word.

Indien erge bloedarmoede of miëlo-onderdrukking plaasvind tydens behandeling met **LODIZ** of by pasiënte met voorafbestaande beenmurgkompromie, bv. hemoglobien <9 g/dl (5,59 mmol/l) of neutrofiele telling <1,0 x 10^9/l (sien **"DOSERING EN GEBRUIKSAANWYSINGS"**), kan die doseringsaanpassing van zidovudien vereis word. Aangesien doseringsaanpassing van **LODIZ** nie moontlik is nie, moet afsonderlike preparate van sidovudien en lamivudien gebruik word. Dokters moet verwys na die individuele verpakkingsbiljette van hierdie middels vir doseringspesifikasies.

Melksuurasidose / hiperlaktatemie:

Gebruik van **LODIZ** kan lei tot potensieel fatale melksuurasidose as gevolg van mitochondriale disfunksie. Skaars, maar potensieel fatale voorkoms van melksuurasidose, in die afwesigheid van hipoksemie, en ernstige hepatomegalie met steatose by pasiënte wat met sidovudien behandel is, is aangemeld. Dit is nie bekend of hierdie gebeure oorsaaklik verband hou met sidovudien nie, maar hulle is by MIV-positiewe pasiënte sonder VIGS aangemeld.

Kliniese kenmerke is nie-spesifiek, en sluit in naarheid, braking, buikpyn, dispnee, moegheid en gewigsverlies.

By pasiënte met verdagte simptome of biochemie, meet die veneuse laktaatvlak (normaal < 2 mmol / l) en die serumbikarbonaat en reageer soos volg:

- Laktaat 2 tot 5 mmol/l met minimum simptome: skakel oor na middels wat minder geneig is om melksuurasidose te veroorsaak.
- Laktaat 5 tot 10 mmol/l met simptome en / of met verminderde standaard bikarbonaat: Staak NRTI's en verander die behandelingopsie. Sodra laktaat gevestig is, gebruik medisyne wat minder geneig is om melksuurasidose te veroorsaak. Sluit ander oorsake uit (bv. sepsis, uremie, diabetiese keto-asidose, tirotoksikose en hipertireose).
- Laktaat > 10 mmol/l: STAAK alle terapie (80 % mortaliteit).

Bogenoemde laktaatwaardes kan nie op pediatriese pasiënte van toepassing wees nie.

Wees versigtig wanneer **LODIZ** toegedien word aan pasiënte met bekende risikofaktore vir lewersiekte.

Behandeling met **LODIZ** moet opgeskort word by enige pasiënt wat kliniese of laboratoriumbevindings ontwikkel wat dui op melksuurasidose of hepatotoksisiteit.

Mitochondriale disfunksie:

Nukleosied- en nukleotiedanaloë het *in vitro* en *in vivo* getoon om 'n veranderlike graad van mitochondriale skade te veroorsaak. Daar is berigte van mitochondriale disfunksie by MIV-negatiewe babas wat *in utero* en / of postnataal blootgestel is aan nukleosiedanaloë. Benewens melksuurasidose / hiperlaktatemie (sien hierbo) sluit ander manifestasies van mitochondriale disfunksie hematologiese afwykings (anemie, neutropenie) en perifere neuropatie in. Sommige latere neurologiese afwykings is aangemeld (hipertonie, stuiptrekkings, abnormale gedrag). Dit is nie bekend of die neurologiese afwykings verbygaande of permanent is nie. Enige fetus wat *in utero* blootgestel word aan nukleosied- en nukleotiedanaloë, selfs MIV-negatiewe babas / kinders, moet kliniese en laboratoriumopvolg hê en moet ten volle ondersoek word vir moontlike mitochondriale disfunksie in die geval van relevante tekens en simptome.

Soos baie nukleosiedanaloë toon lamivudien en sidovudien aktiwiteit by *in vitro* soogdiertoetse, maar nie een van hierdie produkte is mutagenies by bakteriële toetse nie. Lamivudien het geen genotoksiese aktiwiteit by *in vitro* studies getoon nie.

Hoër getalle chromosoombrekings in perifere bloedlimfosiete van VIGS-pasiënte wat sidovudienbehandeling ontvang, is ook waargeneem. Die kliniese implikasies van hierdie bevindings is onduidelik. Beide lamivudien en sidovudien het getoon dat dit die plasenta by reproduktiewe dierstudies oorsteek en bewys het dat dit 'n toename in vroeë embrio-sterftes by die konyn (lamivudien), of by die rot en konyn (sidovudien) veroorsaak. Lamivudien was nie teratogenies by dierestudies nie. Sidovudien gegee aan rotte tydens organogenese by maternale toksiese dosisse, het gelei tot 'n verhoogde voorkoms van misvormings. Fetale afwykings het nie by laer dosisse voorgekom nie.

Met betrekking tot vrugbaarheidstudies by manlike en vroulike rotte, het nie sidovudien of lamivudien bewyse van inkorting getoon nie. Geen inligting is beskikbaar oor die effek van hierdie kombinasie op menslike vrugbaarheid nie. Spermtelling morfologie of motiliteit is nie by mans geraak as gevolg van die gebruik van sidovudien nie. 'n Kankerverwekkende risiko vir mense kan dus nie uitgesluit word nie, weens die kankerverwekkende en mutagenisiteitsdata van diere. Lamivudien het nie enige kankerverwekkende potensiaal getoon in langtermyn-mondkankergenisiteitstudies by rotte en muise nie. Behandelingsverwante effekte was beperk tot laat-verskynende vaginale neoplasmas, by diere wat met sidovudien behandel is. Die relevansie van hierdie gewasse vir mense is steeds onduidelik, en enige teoretiese risiko van kankerverwekkendheid moet gebalanseer word teen die bewese terapeutiese voordeel.

Die relevansie van hierdie bevindings vir beide besmette en onbesmette babas wat aan sidovudien blootgestel is, is onbekend. Swanger vroue wat oorweeg om **LODIZ** te gebruik tydens swangerskap, moet egter van hierdie bevindings ingelig word.

Pankreatitis:

Pankreatitis is waargeneem by sommige pasiënte wat **LODIZ** ontvang. 'n Oorsaaklike verband tussen geneesmiddelbehandeling en onderliggende MIV-siekte kon nie vasgestel word nie. Pankreatitis moet oorweeg word wanneer 'n pasiënt buikpyn, naarheid, braking of verhoogde biochemiese merkers ontwikkel. Staak die gebruik van **LODIZ** totdat die diagnose van pankreatitis uitgesluit is.

Pasiënte met matige tot ernstige nierinkorting:

By pasiënte met matige tot ernstige nierinkorting, word die terminale halfleeftyd van **LODIZ** verhoog as gevolg van verminderde opruiming. Die dosis **LODIZ** moet dus aangepas word (sien **"DOSERING EN GEBRUIKSAANWYSINGS"**).

Lewersiekte:

Gebruik van **LODIZ** kan lei tot hepatomegalie as gevolg van nie-alkoholiese vetterige lewersiekte (hepatiese steatose). Die veiligheid en effektiwiteit van **LODIZ** is nie vasgestel by pasiënte met beduidende onderliggende lewerafwykings / siektes nie. In die geval van gelyktydige antivirale terapie vir hepatitis B of C, raadpleeg asseblief ook die toepaslike verpakkingsbiljette vir hierdie medisyne.

Pasiënte met vooraf bestaande lewerdisfunksie, insluitend chroniese aktiewe hepatitis, het 'n verhoogde frekwensie van lewerfunksie abnormaliteite tydens kombinasie antiretrovirale terapie en moet gemoniteer word. As daar bewyse is van verslegtende lewersiekte by sulke pasiënte, moet die behandeling van die pasiënt tydelik of permanent gestaak word.

Wanneer **LODIZ** toegedien word aan enige pasiënt, veral oorgewig vroue met hepatomegalie, hepatitis of ander bekende risikofaktore vir lewersiekte, moet versigtigheid toegepas word. Hierdie pasiënte moet noukeurig gevolg word tydens behandeling met **LODIZ**.

Pasiënte met MIV en hepatitis B of C virus ko-infeksie:

Pasiënte met chroniese hepatitis B of C en behandel met antiretrovirale terapie het 'n verhoogde risiko vir ernstige en potensieel fatale hepatiese nadelige reaksies.

Mediese praktisyns moet verwys na huidige MIV-behandelingsriglyne vir die optimale bestuur van MIV-infeksie by pasiënte wat ook met hepatitis B virus (HBV) besmet is. In die geval van gelyktydige antivirale terapie vir hepatitis B of C, verwys asseblief ook na die toepaslike verpakkingsbiljette vir hierdie medisyne.

Pasiënte wat mede-besmet is met MIV en HBV wat **LODIZ** stop, moet noukeurig gemoniteer word met beide kliniese en laboratoriumopvolg na behandeling gestaak is. By pasiënte met gevorderde lewersiekte of sirrose word dit nie aanbeveel dat behandeling gestaak word nie, aangesien die verergering van hepatitis na die staking van behandeling kan lei tot hepatiese dekompensasie.

Beëindiging van **LODIZ**-terapie by pasiënte wat beide met MIV en HBV geïnfekteer is, kan geassosieer word met ernstige, akute verergerings van hepatitis.

Lipodistrofie en metaboliese abnormaliteite:

Kombinasie antiretrovirale terapie is geassosieer met die herverdeling / akkumulasie van liggaamsvet, insluitend sentrale vetsug, dorso-servikale vet, vergroting (buffelskof), perifere wegkwyning, gesigswegkwyning, borsvergroting en verhoogde serumlipied- en glukosevlakke by MIV-pasiënte.

Kliniese ondersoek moet evaluering insluit vir fisiese tekens van vetherverdeling. Pasiënte met bewyse van lipodistrofie moet 'n deeglike kardiovaskulêre risikobepaling hê.

Immuun Rekonstitusie Inflammatoriese Sindroom:

Immuun rekonstitusie inflammatoriese sindroom (IRIS) is 'n immunopatologiese reaksie wat voortspruit uit die vinnige herstel van patogeen-spesifieke immuunresponse aan vooraf bestaande antigene gekombineer met immuun disregulasie, wat kort na die aanvang van kombinasie antiretrovirale terapie (cART) plaasvind. Tipies lewer sulke reaksie deur paradoksale verswakking van opportunistiese infeksies wat behandel word of met ontmaskering van 'n asimptomatiese opportunistiese siekte, dikwels met 'n atipiese inflammatoriese voorkoms. IRIS ontwikkel gewoonlik binne die eerste drie maande van die aanvang van ART en kom meer algemeen voor by pasiënte met 'n lae CD4-telling. Algemene voorbeelde van IRIS reaksies op opportunistiese siektes is tuberkulose, sitomegalovirus retinitis en kriptokokkale meningitis.

Toepaslike behandeling van die opportunistiese siekte moet ingestel word of voortgesit word en ART gaan voort. Inflammatoriese manifestasies bedaar gewoonlik na 'n paar weke. Ernstige gevalle kan op glukokortikoïede reageer, maar daar is slegs beperkte bewyse hiervoor by pasiënte met tuberkulose IRIS.

Outo-immuunafwykings (soos Graves se siekte) is ook aangemeld as IRIS-reaksies; hoewel die gerapporteerde tyd tot aanvang egter meer veranderlik is, en hierdie gebeure kan baie maande na aanvang van behandeling voorkom.

Osteonekrose:

Alhoewel die etiologie beskou word om multifaktories te wees (insluitend kortikosteroïedgebruik, alkoholverbruik, ernstige immunosuppressie, hoër liggaamsmassa-indeks), is gevalle van osteonekrose aangemeld, veral by pasiënte met gevorderde MIV-siekte en / of langtermyn blootstelling aan kombinasie antiretrovirale terapie (cART). Pasiënte moet aangeraai word om mediese advies te verkry indien hulle gewrigspyne en pyn, gewrigstyfheid of bewegingsprobleme ervaar.

Opportunistiese infeksies:

Pasiënte wat **LODIZ** ontvang, moet aangeraai word dat hulle kan aanhou om opportunistiese infeksies en ander komplikasies van MIV-infeksie te ontwikkel, en daarom moet hulle onder noukeurige waarneming van gesondheidspraktisyns bly, wat ervare is in die behandeling van pasiënte met verwante MIV-siektes. Gereelde monitering van viruslading en CD4-tellings moet gedoen word.

Die risiko van MIV-oordrag aan ander:

Pasiënte moet in kennis gestel word dat die huidige antiretrovirale terapie, insluitend **LODIZ**, nie die risiko van oordrag van MIV tot ander deur seksuele kontak of bloedbesmetting verhoed nie. Toepaslike voorsorgmaatreëls moet aangewend word.

In gevalle waar doseringsaanpassing nodig is, word aanbeveel dat aparte preparate van lamivudien en sidovudien toegedien word. By hierdie spesiale gevalle moet die dokter verwys na die individuele verpakkingsbiljette vir hierdie middels.

Gelyktydige gebruik van self-toegediende medisyne moet ontmoedig word tydens behandeling met **LODIZ** en pasiënte moet in hierdie verband gewaarsku word (sien **"INTERAKSIES"**).

Geen studies is uitgevoer om die effek van lamivudien of sidovudien op die bestuurvermoëns, of die vermoë om masjinerie te hanteer, te ondersoek nie. Verder, uit die farmakologie van die middels, kan 'n nadelige uitwerking op sulke aktiwiteite nie voorspel word nie. By die oorweging van die pasiënt se vermoë om te bestuur of masjinerie te hanteer, moet die kliniese status van die pasiënt en die nadelige gebeurtenisprofiel van lamivudien en sidovudien in gedagte gehou word.

INTERAKSIES:

Enige interaksies wat met sidovudien en lamivudien individueel aangemeld is, kan ook met **LODIZ** voorkom. Weens die beperkte metabolisme en plasmaproteïenbinding en byna volledige niersuiwering, is die waarskynlikheid van metaboliese interaksies met lamivudien klein. Netso het sidovudien beperkte proteïenbinding, maar word primêr geëlimineer deur lewerkonjugasie na 'n onaktiewe geglukuronideerde metaboliet.

Die interaksies hieronder gelys behoort nie as volledig beskou te word nie, maar is verteenwoordigend van die klasse van middels waarmee sorg uitgeoefen behoort te word.

Interaksies relevant tot lamivudien:

Moontlike interaksies met ander middels wat saam met **LODIZ** toegedien word, behoort ondersoek te word, veral wanneer die hoofroete van eliminasie aktiewe nieruitskeiding is, veral via die kationiese transportsisteem bv. trimetopriem. Die nukleosiedanaloë (bv. sidovudien, didanosien en salsitabien) en ander middels (bv. ranitidien, simetidien) word gedeeltelik deur hierdie meganisme geëlimineer en dit is aangetoon dat hulle geen interaksie met lamivudien toon nie.

Verwys asseblief na die Farmakokinetika afdeling vir volle besonderhede van die interaksie van lamivudien met ander antiretrovirusmiddels.

Dit is aangemeld dat die toediening van profilaktiese dosisse van kotrimoksasool tot 'n toename in die konsentrasie van lamivudien gelei het. Dit kan aan die trimetopriemkomponent toegeskryf word, aangesien die sulfametoksasoolkomponent nie gereageer het nie. Geen doseringsaanpassing van lamivudien is nodig, tensy die pasiënt aan belemmerde nierfunksie ly (sien "**DOSERING EN GEBRUIKSAANWYSINGS"**).

Pasiënte behoort klinies gemonitor te word wanneer gelyktydige toediening van kotrimoksasool geregverdig word. Hoë dosisse van kotrimoksasool in kombinasie met **LODIZ** vir die behandeling van Pneumocystis carinii pneumonia (PCP) en toksoplasmose behoort vermy te word. Die dosisse wat bestudeer is toon aan dat lamivudien geen effek op die farmakokinetika van kotrimoksasool het nie.

Totdat verdere inligting beskikbaar word, word die medetoediening van lamivudien met intraveneuse gansiklovir of foskarnet nie aanbeveel nie.

Interaksies relevant tot sidovudien:

Sidovudien het geen effek op die farmakokinetika van lamivudien nie. 'n Effense toename in K_{maks} (28 %) is vir sidovudien waargeneem wanneer dit met lamivudien toegedien word. Die algehele blootstelling (AOK) het nie beduidend verander nie.

Die medetoediening van sidovudien en rifampisien verlaag die AOK van sidovudien met 48 % ± 34 %. Die kliniese betekenis hiervan is egter onbekend.

By sommige pasiënte wat sidovudien ontvang het, is dit aangemeld dat die bloedvlakke van fenitoïen laag was, terwyl dit by een pasiënt hoog was. Hierdie waarnemings impliseer dat fenitoïenkonsentrasies noukeurig gemonitor behoort te word by pasiënte wat **LODIZ** in kombinasie met fenitoïen ontvang.

Die gebruik van parasetamol gedurende behandeling met sidovudien in 'n plasebobeheerde proef is met 'n toename in die voorkoms van neutropenie geassosieer, veral na chroniese terapie. Die beskikbare farmakokinetiese data toon egter aan dat parasetamol teen die dosisse wat bestudeer is, nie die plasmavlakke van sidovudien of sy glukuroniedmetaboliet verhoog nie.

Die volgende middels, insluitend maar nie beperk tot, kan die metabolisme van sidovudien verander deur glukuronidasie kompeterend te inhibeer, of direk mikrosomale metabolisme in die lewer te inhibeer: aspirien, kodeïen, morfien, indometasien, ketoprofen, naproksen, oksasepam, lorasepam, simetidien, klofibraat, dapsoon en isoprinosien. Die moontlikheid van middelinteraksies behoort oorweeg te word voordat sulke middels, veral vir chroniese terapie, in kombinasie met **LODIZ** gebruik word.

Die risiko van newe-effekte tot sidovudien kan ook toeneem met meegaande terapie, veral akute terapie, met potensieel nefrotoksiese of miëlo-onderdrukkende middels (bv. sistemiese pentamidien, dapsoon, pirimetamien, kotrimoksasool, amfoteresien, flukitosien, gansiklovir, interferon, vinkristien, vinblastien en doksorubisien). Ekstra sorg moet geneem word in die monitering van nierfunksie en hematologiese parameters en indien nodig, behoort die dosis van een of meer van die middels verminder te word, wanneer die meegaande terapie met **LODIZ** en enige van hierdie middels nodig is.

In vitro is die kombinasie van sidovudien met ribavirien of stavudien antagonisties. Die gelyktydige gebruik van ribavirien of stavudien saam met **LODIZ** behoort vermy te word (sien "**KONTRA-INDIKASIES"**).

Die gelyktydige gebruik van profilaktiese antimikrobiese terapie behoort moontlik oorweeg te word, aangesien sommige pasiënte wat **LODIZ** ontvang, kan aanhou om opportunistiese infeksies op te doen. Hierdie genoemde profilakse het pirimetamien, kotrimoksasool, pentamidien in aerosolvorm en asiklovir ingesluit. Die beperkte data uit kliniese proewe toon nie 'n beduidende toename in die risiko van newe-effekte tot sidovudien met hierdie middels aan nie.

Deur die afname in glukuronidasie wil dit uit beperkte data voorkom asof probenesied die halfleeftyd en area onder die plasmakonsentrasiekurwe van sidovudien laat toeneem. In die teenwoordigheid van probenesied, word die nieruitskeiding van die glukuronied (en moontlik sidovudien as sulks) verminder.

MENSLIKE VOORTPLANTING:

Die veiligheid van lamivudien by menslike swangerskap is nie vasgestel nie. Derhalwe word behandeling gedurende die eerste trimester van swangerskap nie aanbeveel nie.

Dit is aangetoon dat die gebruik van sidovudien by swanger vroue, met die daaropvolgende behandeling van die nuutgebore baba, die koers van moeder-fetusoordraging van MIV verminder. Dit is egter nie vir lamivudien vasgestel nie. Gevolglik behoort die toediening van **LODIZ** gedurende swangerskap slegs oorweeg te word indien die verwagte voordele opweeg teen enige moontlike risiko's.

Studies by lakterende rotte het getoon dat, na orale toediening, lamivudien en sidovudien in die melk uitgeskei is. Dit is nie bekend of lamivudien of sidovudien in menslike melk uitgeskei word nie. Aangesien hierdie middels na die borsmelk kan beweeg, word dit aanbeveel dat moeders wat **LODIZ** gebruik, nie hul babas borsvoed nie.

DOSERING EN GEBRUIKSAANWYSINGS:

Volwassenes en kinders ouer as 12 jaar:

Die aanbevole dosis: een tablet twee keer per dag.

LODIZ kan met of sonder voedsel toegedien word.

'n Dokter met ondervinding in die bestuur van MIV-infeksie behoort terapie te inisieer. Tydens kombinasieterapie met ander antiretrovirusmiddels behoort die verpakkingsbiljette van die spesifieke middel vir inligting geraadpleeg te word.

Belemmerde nierfunksie:

Weens 'n afname in suiwering by pasiënte met belemmerde nierfunksie, is die konsentrasies van lamivudien en sidovudien hoër. Daarom, aangesien die aanpassing van die doserings van hierdie middels nodig kan wees, word dit aanbeveel dat aparte preparate van lamivudien en sidovudien toegedien word aan pasiënte met vertraagde nierfunksie (kreatiniensuiwering 50 ml/min). Die verpakkingsbiljette van die spesifieke preparate moet vir volledige besonderhede van hierdie doseringsaanpassings geraadpleeg word.

Belemmerde lewerfunksie:

Die invloed van belemmerde lewerfunksie op lamivudienvlakke is nog nie heeltemal duidelik nie. Suiwering van lamivudien vind hoofsaaklik deur die niere plaas. Gebaseer op voorlopige veiligheidsdata is geen aanpassing van die dosering nodig nie. Lamivudien behoort met sorg gebruik te word by pasiënte met hepatomegalie of ander risikofaktore vir lewersiekte. Beperkte data by pasiënte met sirrose dui daarop dat akkumulasie van sidovudien weens 'n afname in glukuronidasie by pasiënte met belemmerde lewerfunksie kan voorkom. Daarom, aangesien doseringsaanpassings vir sidovudien nodig kan wees, word dit aanbeveel dat aparte lamivudien- en sidovudienpreparate aan pasiënte met erg belemmerde lewerfunksie toegedien word. Die verpakkingsbiljet vir sidovudien behoort vir volle besonderhede van doseringsaanpassings geraadpleeg te word.

Doseringsaanpassings by pasiënte met hematologiese newe-effekte:

Doseringsaanpassing van sidovudien kan nodig wees indien die hemoglobienvlakke onder 9 g/dl of 5,59 mmol/l, of die neutrofieltelling onder 1,0 x 10^9/l daal (sien "**KONTRA-INDIKASIES"**). Dit is meer waarskynlik by pasiënte met swak beenmurgreserwes voor behandeling, veral pasiënte met gevorderde MIV-siekte. Aangesien aanpassing van die **LODIZ** dosering nie moontlik is nie, behoort aparte sidovudien- en lamivudienpreparate gebruik te word. Dokters behoort na die individuele verpakkingsbiljette te verwys.

Dosering by bejaardes:

Weens ouderdomsverwante veranderinge soos 'n afname in nierfunksie en verandering van hematologiese parameters, word spesiale sorg vir bejaarde pasiënte aanbeveel.

NEWE-EFFEKTE:

Newe-effekte is aangemeld gedurende terapie vir MIV-siekte met lamivudien en sidovudien, apart of in kombinasie. Met menige van hierdie gebeurtenisse is dit nie bekend of hulle met lamivudien, sidovudien of met die wye reeks middels wat in die bestuur van MIV-siekte gebruik word, verband hou nie, of dat hulle die gevolg van die onderliggende siekteproses is.

Aangesien **LODIZ** lamivudien en sidovudien bevat, kan die tipe en graad van erns van newe-effekte van elkeen van die middels verwag word. Daar bestaan geen bewys van sinergistiese toksisiteit na die gelyktydige toediening van die twee middels nie.

Lamivudien: Die newe-effekte wat aangemeld is, is:

Afwykings van die senuweestelsel

Dikwels: Hoofpyn, slaaploosheid.

Minder dikwels: Alhoewel geen verwantskap met die lamivudiendosis aangemeld is nie, is gevalle van perifere neuropatie (of parestesie) aangeteken.

Muskuloskeletale-, bindweefsel en beenafwykings

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: malaise, moegheid, muskuloskeletale pyn.

Gastroïntestinale afwykings

Dikwels: Naarheid, diarree, braking, buikpyn of krampe.

Respiratoriese-, bors en mediastinale afwykings

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Hoes, neussimptome.

Endokriene afwykings

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Alhoewel geen verwantskap met lamivudien aangemeld is nie, is gevalle van pankreatitis aangemeld.

Afwykings van die bloed en limfatiese sisteem

Dikwels: Anemie en neutropenie (beide af en toe akuut) het in kombinasie met sidovudien voorgekom. Trombositopenie is aangemeld.

Ondersoeke

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Verbygaande toenames in lewerensieme (AST, ALT) en toenames in serumamilase is aangemeld.

Sidovudien:

Afwykings van die bloed en limfatiese sisteem

Anemie (wat bloedoortapping kan noodsaak), neutropenie en leukopenie is as die mees ernstige newe-effekte aangemeld. Hierdie newe-effekte kom meer dikwels teen hoër doserings (1 200 tot 1 500 mg/dag) voor, asook by pasiënte met gevorderde MIV-siekte (veral met swak beenmurgreserwe voor behandeling), en veral by pasiënte met CD4 seltellings van < 100/mm³. 'n Vermindering van dosis of staking van terapie kan noodsaaklik word (sien "**DOSERING EN GEBRUIKSAANWYSINGS**").

Newe-effekte is aangemeld by pasiënte wie se neutrofieltellings, hemoglobienvlakke en serum vitamien B_{12} vlakke laag is aan die begin van sidovudien terapie, en by pasiënte wat gelyktydiglik parasetamol gebruik (sien "**INTERAKSIES"**).

Gastroïntestinale afwykings

Dikwels: Naarheid, braking, anoreksie, buikpyn, dispepsie.

Afwykings van die senuweestelsel

Dikwels: Hoofpyn, parestesie, astenie, slaaploosheid.

Afwykings van die vel en subkutane weefsels

Dikwels: Uitslag.

Muskuloskeletale-, bindweefsel en beenafwykings

Dikwels: Mialgie, malaise.

Naarheid het aansienlik meer dikwels by alle studies by pasiënte wat sidovudien ontvang het, voorgekom. Dit is aangemeld dat die ander newe-effekte nie konsistent meer dikwels as by die plasebo-ontvangers voorgekom het nie. Braking, anoreksie, malaise en astenie het meer dikwels by sidovudienbehandelde pasiënte met vroeë MIV- siekte voorgekom, terwyl erge hoofpyn, mialgie en slaaploosheid meer dikwels by die sidovudienbehandelde pasiënte met gevorderde MIV-siekte voorgekom het.

Algemene afwykings en kondisies by die plek van toediening

Dikwels: Koors.

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Slaapsug, diarree, duiseligheid, sweet, dispnee, winderigheid, smaakafwyking, borspyn, verlies aan geestelike skerpheid, angs, urienfrekwensie, depressie, algemene pyn, kouerillings, hoes, urtikarie, pruritus en 'n griepagtige sindroom is as ander newe-effekte wat met die gebruik van **LODIZ** geassosieer word, aangemeld.

Die voorkoms van hierdie en ander minder dikwelse newe-effekte was soortgelyk by beide die sidovudien- en plasebobehandelde pasiënte. Die voorkoms van naarheid en ander dikwels aangemelde newe-effekte het konsistent met verloop van tyd gedurende die eerste paar weke van terapie met sidovudien verminder. Dit is aangetoon met beskikbare data van beide plasebobeheerde en ope-etiket studies.

Die verwantskap tussen die volgende gebeurtenisse wat aangemeld is, en die gebruik van sidovudien, is moeilik om te evalueer as die medies gekompliseerde situasies wat kenmerkend van gevorderde MIV-siekte is, in ag geneem word (sien **"WAARSKUWINGS en SPESIALE VOORSORGMAATREËLS"**).

Hepatobiliêre afwykings

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Melksuurasidose in die afwesigheid van hipoksemie, lewerafwykings soos erge hepatomegalie met steatose.

Muskuloskeletale-, bindweefsel en beenafwykings

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Miopatie.

Afwykings van die bloed en limfatiese sisteem

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Pansitopenie met beenmurghipoplasie en geïsoleerde trombositopenie.

Ondersoeke

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Verhoogde bloedvlakke van lewerensieme en bilirubien.

Endokriene afwykings

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Pankreatitis.

Muskuloskeletale-, bindweefsel en beenafwykings

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Pigmentering van die naels, vel en mondslymvlies.

Afwykings van die senuweestelsel

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: By pasiënte wat ope-etiket terapie met sidovudien ontvang, is stuiptrekkings en ander serebrale gebeurtenisse ook aangemeld. Die voordelige effek van sidovudien op MIV-geassosieerde neurologiese afwykings word oor die algemeen gestaaf deur die hoeveelheid bewyse.

Indien die graad van erns van die simptome dit regverdig, kan 'n vermindering of staking van sidovudien terapie help in die beoordeling en bestuur van hierdie kondisies. Die gebruik van **LODIZ** behoort gestaak te word en aparte preparate van sidovudien en lamivudien behoort toegedien te word indien die simptome ondraaglik word (sien **"WAARSKUWINGS en SPESIALE VOORSORGMAATREËLS"**).

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:

Daar bestaan geen ondervinding van oordosering met **LODIZ** nie. Daar is beperkte data beskikbaar oor die gevolge van die inname van akute oordosisse van lamivudien en sidovudien by mense. Alle pasiënte het herstel, geen sterftes het voorgekom nie. Na oordosering is geen spesifieke tekens of simptome geïdentifiseer nie.

Behandeling van oordosering:

In die geval van oordosering behoort die pasiënt vir bewys van toksisiteit gemonitor te word (sien "**NEWE-EFFEKTE" en "WAARSKUWINGS en SPESIALE VOORSORGMAATREËLS"**) en waar nodig, behoort die standaard ondersteunende behandeling toegepas te word. Aangesien lamivudien dialiseerbaar is, kan aanhoudende hemodialise by die behandeling van oordosering gebruik word, alhoewel dit nog nie bestudeer is nie.

Dit wil voorkom asof hemodialise en peritoneale dialise 'n beperkte effek op die eliminasie van sidovudien het. Dit verbeter egter die eliminasie van die glukuroniedmetaboliet. Dokters behoort na die individuele verpakkingsbiljette van lamivudien en sidovudien vir dosisaanwysings te verwys. Pasiënte by wie doelbewuste oordosis bevestig of vermoed word, behoort vir psigiatriese evaluasie verwys te word.

IDENTIFIKASIE:

Wit, gemodifiseerde kapsuulvormige, bikonvekse filmbedekte tablette met 'C' en '60' op die een kant gedruk, en gewoon aan die ander kant.

AANBIEDING:

1. 60 tablette verpak in 'n wit 110 ml HDPE houer (swaargewig), verseël met 'n dop met 'n induksieseëlprop.
2. 60 tablette verpak in 'n wit, ronde 75 ml HDPE houer (swaargewig), met 'n geribde polipropileendop met 'n induksieseëlprop.

Nie alle verpakkings en pakgroottes word noodwendig bemark nie.

BEWARINGSINSTRUKSIES:

Bewaar teen of benede 30 °C. Beskerm teen lig en vogtigheid.

HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER:

A40/20.2.8/0381

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE:

Novagen Pharma (Pty) Ltd
Kantoor 2, Sovereignrylaan 100
Route 21 Corporate Park
Nellmapiusrylaan
Irene - Pretoria
Suid-Afrika

DATUM VAN PUBLIKASIE VAN HIERDIE PROFESSIONELE INLIGTING:

Datum van registrasie: 11 Augustus 2006

Datum van laaste hersiening van die teks soos goedgekeur deur die Raad: 11 Augustus 2006

Datum van kennisgewing met betrekking tot gewysigde Reg. 9 en 10: 02 Februarie 2015

P1518117

DETACH BEFORE DISPENSING

PASIËNTINLIGTIGINGSBILJET

SKEDULERINGSTATUS

S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM

LODIZ (Tablet)

Lamivudien/Sidovudien.

Lees die hele biljet voordat u begin om LODIZ te gebruik.

- Hou hierdie biljet. U mag dit moontlik weer wil lees.
- Indien u enige verdere vrae het, raadpleeg asseblief u dokter of apteker.
- **LODIZ** is vir u persoonlik voorgeskryf en u moet nie u medisyne met ander mense deel nie. Dit kan hulle skade aandoen, al het hulle ook dieselfde simptome as u.

1. WAT LODIZ BEVAT

- Die aktiewe bestanddele is lamivudien en sidovudien. Elke filmbedekte tablet bevat 150 mg lamivudien en 300 mg sidovudien.
- Die ander bestanddele is: kolloïdale silikoondioksied, magnesiumstearaat, mikrokristallyne sellulose, natriumstyselglikolaat, Opadry 13B58802 IHWit (hipromellose, titaandioksied, poliëtileenglikol 400, polisorbaat 80). Suikervry.

2. WAARVOOR LODIZ GEBRUIK WORD

LODIZ-tablette word aangedui as deel van 'n antiretrovirale kombinasie-terapie vir die behandeling van Menslike Immuniteitsgebrekvirus- (MIV-) geïnfekteerde volwassenes en kinders ouer as 12 jaar, met progressiewe immuuntekort (CD4-waarde ≤ 500 selle/mm³).

3. VOORDAT U LODIZ NEEM

Vermy die gebruik van LODIZ in die volgende situasies:

- Indien u hipersensitief (allergies) is vir lamivudien of sidovudien of enige ander bestanddele van **LODIZ**-tablette nie.
- Nie aanbeveel vir kinders jonger as 12 jaar oud nie. Onvoldoende data is beskikbaar.
- Pasiënte met abnormaal lae neutrofieltellings (< 0,75 x 10^9/l), of abnormaal lae hemoglobienvlakke (< 7,5 g/dl).
- *In vitro* is die kombinasie van sidovudien met óf ribavirien óf stavudien antagonisties. Die gelyktydige gebruik van óf ribavirien óf stavudien saam met **LODIZ** behoort vermy te word.

Neem spesiale voorsorg met LODIZ:

- U kan 'n potensieel noodlottige kondisie genaamd melksuurasidose ontwikkel terwyl u **LODIZ** gebruik. Stel onmiddellik u dokter of ander gesondheidsbeampte in kennis indien u enige van die volgende simptome ontwikkel: naarheid, braking, buikpyn, dispnee, moegheid en gewigsverlies. U dokter sal bloedtoetse uitvoer en u dienooreenkomstig behandel.
- Indien u sou swanger raak terwyl u **LODIZ** gebruik, kan u baba bloed- en senuweestelselafwykings ontwikkel. U dokter sal u baba se toestand monitor.
- Pankreatitis (inflammasie van die pankreas) is waargeneem by sommige pasiënte wat behandeling ontvang met **LODIZ.** Raadpleeg onmiddellik u dokter of ander gesondheidsbeampte indien u abdominale pyn, naarheid of braking ontwikkel. U dokter sal u behandeling met **LODIZ** staak totdat die diagnose van pankreatitis uitgesluit is.
- Indien u aan nierafwykings ly sal u dokter of gesondheidsbeampte u **LODIZ**-dosering moet aanpas.
- U kan lewerafwykings ontwikkel terwyl u **LODIZ** gebruik. Stel u dokter of gesondheidsbeampte in kennis as u aan 'n voorafbestaande lewersiekte, insluitend Hepatitis B of C, ly.
  Moet nie die gebruik van **LODIZ** staak as u met beide MIV en Hepatitis geïnfekteer is nie, aangesien dit kan lei tot die verergering van die Hepatitis-infeksie.
- U kan moontlik 'n kondisie genaamd lipodistrofie ontwikkel terwyl u **LODIZ** gebruik. Stel u dokter of gesondheidsbeampte in kennis as u enige van die volgende veranderings opmerk: die herverspreiding van u liggaamsvet (bv. die akkumulasie van vet rondom die buik- of maagarea, agter op die nek en tussen die skouers, naamlik 'n buffelskof, of die ontwikkeling van groter borste), die wegkwyning van die arms, bene en gesigspiere, asook verhoogde bloedglukosevlakke en lipiedwaardes.
- Indien u vir die eerste keer **LODIZ** gebruik, kan u moontlik binne die eerste paar maande van behandeling 'n kondisie ontwikkel wat bekend staan as Immuunrekonstitusie-inflammatoriese sindroom (IRIS). Hierdie kondisie kan opportunistiese infeksies wat alreeds behandel word, laat vererger, of opportunistiese infeksies wat voorheen geen simptome getoon het nie, ontmasker. Stel u dokter of gesondheidsbeampte in kennis indien u algemene gesondheid verswak, of indien u vermoed dat u 'n infeksie het. U moet nie die gebruik van **LODIZ** staak nie. U dokter sal die infeksie toepaslik behandel.
- U kan 'n kondisie bekend as osteonekrose ontwikkel terwyl u **LODIZ** gebruik. U word aangeraai om mediese advies in te win indien u pynlike en stywe gewrigte, of moeisame beweging ervaar.
- U kan steeds opportunistiese infeksies, asook ander komplikasies van MIV-infeksie ontwikkel terwyl u **LODIZ** gebruik. U behoort steeds noukeurig gemonitor te word deur 'n gesondheidsbeampte wat ervare is in die behandeling van pasiënte met gepaardgaande MIV-siektes. Gereelde monitering van virale lading en CD4-tellings moet gedoen word.
- U loop steeds die risiko om MIV aan ander oor te dra deur seksuele kontak of bloedkontaminasie terwyl u tans antiretrovirale behandeling ontvang, onder andere terapie met **LODIZ**. Gepaste voorsorgmaatreëls behoort voortdurend toegepas te word.

Die neem van LODIZ saam met voedsel en vloeistof:

LODIZ-tablette kan met of sonder voedsel geneem word.

Swangerskap en borsvoeding:

Die veiligheid van lamivudien by menslike swangerskap is nie vasgestel nie. Derhalwe word behandeling gedurende die eerste trimester van swangerskap nie aanbeveel nie.

Daar is getoon dat die gebruik van sidovudien by swanger vroue, met die daaropvolgende behandeling van die pasgebore baba, die voorkoms van moeder-fetus-oordraging van MIV verminder. Dit is egter nie vir lamivudien vasgestel nie. Gevolglik behoort die toediening van **LODIZ** gedurende swangerskap slegs oorweeg te word indien die verwagte voordele enige moontlike risiko's oorskadu.

Studies by lakterende rotte het getoon dat lamivudien en sidovudien, na orale toediening, in die melk uitgeskei is. Dit is nie bekend of lamivudien of sidovudien in menslike melk uitgeskei word nie. Aangesien hierdie middels oorgedra kan word na die borsmelk, word dit aanbeveel dat moeders wat **LODIZ** gebruik nie hul babas borsvoed nie.

As u swanger is of u baba borsvoed, moet u asseblief u dokter, apteker of ander gesondheidsbeampte raadpleeg voordat u **LODIZ** neem.

Die neem van ander medisyne saam met LODIZ:

Stel altyd u gesondheidsbeampte in kennis as u ander medikasie gebruik (dit sluit komplimentêre en tradisionele medisyne in).

LODIZ reageer met trimetoprim.

Die toediening van profilaktiese dosisse van kotrimoksasool veroorsaak 'n verhoogde konsentrasie van lamivudien in die bloedstroom. U dosis kan aangepas word indien u dokter bevestig dat u aan moontlike nierinkorting ly.

U dokter sal die fenitoïenkonsentrasies in u bloedstroom noukeurig monitor indien u hierdie middel gebruik.

Aspirien, kodeïen, morfien, indometasien, ketoprofeen, naproksen, oksasepam, lorasepam, simetidien, klofibraat, dapsoon en isoprinosien kan inmeng met die metabolisme van sidovudien. As u tans enige van hierdie middels in kombinasie met **LODIZ** gebruik, sal u dokter enige beduidende uitwerking monitor. Indien u tans sistemiese pentamidien, dapsoon, pirimetamien, kotrimoksasool, amfoteresien, flusitosien, gansiklovir, interferon, vinkristien of vinblastien gebruik, verhoog die risiko vir potensieel ernstige newe-effekte veroorsaak deur sidovudien. U dokter sal u nier- en hematologiese parameters monitor en enige nodige doseringsaanpassings oorweeg.

4. HOE OM LODIZ TE NEEM

Moet nooit u voorgeskrewe medikasie met iemand anders deel nie.

Neem **LODIZ** altyd presies soos deur u dokter voorgeskryf. As u onseker is, moet u dit asseblief met u dokter of apteker bevestig. As u van mening is dat die uitwerking van **LODIZ** te sterk of te swak is, raadpleeg u dokter of apteker.

Volwassenes en kinders oor die ouderdom van 12 jaar:

- Die aanbevole dosis: een tablet wat twee maal per dag oraal toegedien word.
- Die terapie behoort deur 'n dokter waargeneem te word met ondervinding in die behandeling van MIV-infeksie. **LODIZ**-tablette kan met of sonder voedsel geneem word.
- 'n Doseringsaanpassing kan nodig wees indien u dokter bevestig dat u aan belemmerde nier- en lewerfunksie ly of indien u 'n verhoogde risiko loop vir hematologiese newe-effekte.

As u te veel LODIZ geneem het:

In die geval van oordosering behoort die pasiënt gemonitor en die standaard ondersteunende behandeling toegepas te word indien nodig. In die geval van oordosering, moet u u dokter of apteker raadpleeg. As hulle nie beskikbaar is nie, kontak u naaste hospitaal of gifbeheersentrum.

As u vergeet om LODIZ te neem:

Moenie die dosis verdubbel om vir die oorgeslane individuele dosis te vergoed nie.

5. MOONTLIKE NEWE-EFFEKTE

LODIZ kan newe-effekte veroorsaak.

LODIZ is 'n kombinasie van beide lamivudien en sidovudien en dus kan elkeen van hierdie middels newe-effekte veroorsaak.

Lamivudien: Die volgende newe-effekte is aangemeld:

Afwykings van die senuweestelsel:

Dikwels: Hoofpyn, slapeloosheid.

Minder dikwels: Alhoewel daar geen verwantskap met die lamivudiendosis aangemeld is nie, is gevalle van perifere neuropatie (of parestesie) aangeteken.

Muskuloskeletale-, bindweefsel en beenafwykings:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: malaise, moegheid, muskuloskeletale pyn.

Gastroïntestinale afwykings:

Dikwels: Naarheid, diarree, braking, buikpyn of krampe.

Respiratoriese-, bors en mediastinale afwykings:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Hoes, nasale simptome.

Endokriene afwykings:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Alhoewel daar geen verwantskap met die lamivudiendosis aangemeld is nie, is gevalle van pankreatitis aangemeld.

Afwykings van die bloed en limfatiese sisteem:

Dikwels: Anemie en neutropenie (beide soms akuut) het in kombinasie met sidovudien voorgekom. Trombositopenie is aangemeld.

Ondersoeke:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Verbygaande toenames in lewerensieme (AST, ALT). Toenames in serumamilase is aangemeld.

Sidovudien: Die volgende newe-effekte is aangemeld:

Afwykings van die bloed en limfatiese sisteem

Anemie (wat 'n bloedoortapping kan vereis), neutropenie en leukopenie is as die mees ernstige newe-effekte aangemeld. Hierdie newe-effekte kom meer dikwels teen hoër dosisse (1 200 tot 1 500 mg/dag) voor, asook by pasiënte met gevorderde MIV-siekte (veral tydens die voorkoms van swak beenmurgreserwe voor aanvang van behandeling), en veral by pasiënte met CD4-seltellings van < 100 mm³. 'n Vermindering van die dosis of staking van terapie kan noodsaaklik word.

Newe-effekte is aangemeld by pasiënte wie se neutrofieltellings, hemoglobienvlakke en serum-vitamien B_{12}-vlakke laag was aan die begin van sidovudien-terapie, en by pasiënte wat terselfdertyd parasetamol gebruik.

Gastroïntestinale afwykings:

Dikwels: Naarheid, braking, anoreksie, buikpyn, dispepsie.

Afwykings van die senuweestelsel:

Dikwels: Hoofpyn, parestesie, astenie, slapeloosheid.

Afwykings van die vel en subkutane weefsels:

Dikwels: Uitslag.

Muskuloskeletale-, bindweefsel en beenafwykings

Dikwels: Mialgie, malaise.

Naarheid het aansienlik meer dikwels voorgekom van alle studies van pasiënte wat sidovudien ontvang het. Daar is nie konsekwent aangemeld dat die ander newe-effekte meer dikwels voorgekom het as in die plasebo-ontvangers nie. Braking, anoreksie, malaise en astenie het meer dikwels by sidovudien-behandelde pasiënte met vroeë MIV-siekte voorgekom, terwyl erge hoofpyn, mialgie en slapeloosheid meer dikwels by die sidovudien-behandelde pasiënte met gevorderde MIV-siekte voorgekom het.

Algemene afwykings en kondisies by die plek van toediening:

Dikwels: Koors.

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Slaapsug, diarree, duiseligheid, sweet, dispnee, winderigheid, smaakafwyking, borspyn, verlies aan flink verstandelike vermoëns, angs, urinêre frekwensie, depressie, algemene pyn, koue rillings, hoes, urtikarie, pruritus en 'n griepagtige sindroom; hierdie simptome is as verdere newe-effekte, wat met die gebruik van **LODIZ** geassosieer word, aangemeld.

Die voorkoms van hierdie en ander minder algemene newe-effekte was soortgelyk by beide die sidovudien en plasebo-behandelde pasiënte. Die insidensie van naarheid en ander algemeen-aangemelde kliniese newe-effekte het met verloop van tyd konstant verminder gedurende die eerste paar weke van terapie met sidovudien. Dit is aangetoon met beskikbare data van beide plasebo-beheerde en oop kliniese proefstudies.

Die verwantskap tussen die volgende newe-effekte wat aangemeld is, en die gebruik van sidovudien, is moeilik om te evalueer indien die medies-gekompliseerde situasies, wat kenmerkend van gevorderde MIV-siekte is, in ag geneem word.

Hepatobiliêre afwykings:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Melksuurasidose in die afwesigheid van hipoksemie, lewerafwykings soos erge hepatomegalie met steatose.

Muskuloskeletale-, bindweefsel en beenafwykings:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Miopatie.

Afwykings van die bloed en limfatiese sisteem:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Pansitopenie met beenmurg-hipoplasie en geïsoleerde trombositopenie.

Ondersoeke:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Verhoogde bloedvlakke van lewerensieme en bilirubien.

Endokriene afwykings:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Pankreatitis.

Muskuloskeletale-, bindweefsel en beenafwykings:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: Pigmentering van die naels, vel en mondslymvlies.

Afwykings van die senuweestelsel:

Die volgende newe-effekte is aangemeld, maar die frekwensies daarvan is onbekend: By pasiënte wat oop kliniese proefterapie met sidovudien ontvang, is stuiptrekkings en ander serebrale gebeurtenisse ook aangemeld. Die voordelige effek van sidovudien op MIV-geassosieerde neurologiese afwykings word oor die algemeen gestaaf deur die hoeveelheid bewyse.

Indien die ernstigheidsgraad van die simptome dit regverdig, kan 'n vermindering of staking van sidovudienterapie help in die beoordeling en bestuur van hierdie kondisies. Die gebruik van **LODIZ** behoort gestaak en aparte preparate van sidovudien en lamivudien toegedien te word, indien die simptome ondraaglik sou raak.

Nie alle aangemelde newe-effekte van **LODIZ** is ingesluit in hierdie biljet nie. Sou u algemene gesondheid verswak of u enige ongewensde newe-effekte ervaar terwyl u **LODIZ** gebruik, moet u asseblief u dokter, apteker of ander gesondheidsbeampte raadpleeg vir advies.

As u enige newe-effekte waarneem wat nie in hierdie biljet genoem word nie, moet u asseblief u dokter of apteker in kennis stel.

6. BERGING EN WEGGOOI VAN LODIZ:

Bewaar teen of benede 30 °C. Beskerm teen lig en vogtigheid.

HOU BUITE BEREIK VAN KINDERS.

Neem alle ongebruikte medisyne terug na u apteker.

Moenie enige ongebruikte medisyne in 'n drein of rioleringstelsel (bv. toilet) wegspoel nie.

7. AANBIEDING VAN LODIZ:

1. 60 tablette word in 'n wit, 110 ml HDPE-houer (swaargewig) verpak en bedek met 'n dop wat 'n induksieseëlprop bevat.
2. 60 tablette word in 'n wit, ronde, 75 ml HDPE-houer (swaargewig) verpak, met 'n geriffelde polipropileendop wat 'n induksieseëlprop bevat.

Nie alle verpakkings en pakgroottes word noodwendig bemark nie.

8. IDENTIFIKASIE VAN LODIZ:

Wit, gemodifiseerde kapsuulvormige, bikonvekse, filmbedekte tablette met 'C' en '60' op die een kant gedruk, en gewoon aan die ander kant.

9. REGISTRASIENOMMER

A40/20.2.8/0381

10. NAAM, BESIGHEIDSADRES EN TELEFOONNOMMER VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE

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11. DATUM VAN PUBLIKASIE VAN HIERDIE PASIËNTINLIGTINGSBILJET

Datum van registrasie: 11 Augustus 2006

Datum van die laaste hersiening van die teks soos goedgekeur deur die Raad: 11 Augustus 2006

Datum van kennisgewing ten opsigte van gewysigde Reg. 9 en 10: 02 Februarie 2015