Vicondine®
Lamivudine

FORMS AND PRESENTATION
Vicondine®: Film coated tablets: Jar of 60 FCT.
COMPOSITION
Vicondine®: Each film coated tablet contains Lamivudine 150mg.
Excipients: microcrystalline cellulose, sodium starch glycolate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, polysorbate.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Therapeutic class: Antivirals for systemic use.
ATC code: J05AF05.
Lamivudine is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolized intracellularly to the active moiety, Lamivudine 5'-Triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication in vitro; it is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.
Pharmacokinetic properties
Absorption
Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral Lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour.
Co-administration of Lamivudine with food results in a delay of t_{max} and a lower C_{max} (decreased by 47%). However, the extent (based on the AUC) of Lamivudine absorbed is not influenced.
Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.
Co-administration of zidovudine results in a 13% increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.
Distribution
From intravenous studies, the mean volume of distribution is 1.3 l/kg. The observed half-life of elimination is 5 to 7 hours. The mean systemic clearance of Lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%) via the organic cationic transport system.
Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 16% - 36% to serum albumin in in vitro studies).
Limited data show that Lamivudine penetrates the central nervous system and reaches the cerebro-spinal fluid (CSF). The mean ratio CSF/serum Lamivudine concentration 2-4 hours after oral administration was approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.
Biotransformation
The active moiety, intracellular Lamivudine Triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma Lamivudine half-life (5 to 7 hours).
Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions of Lamivudine with other medicinal products is low due to the small extent of hepatic metabolism (5-10%) and low plasma protein binding.
Elimination
Studies in patients with renal impairment show Lamivudine elimination is affected by renal dysfunction.
An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40% increase in Lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with Lamivudine in patients with renal impairment should be carefully assessed.
INDICATIONS
Vicondine® is indicated as part of antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children.
CONTRAINDICATIONS
- Hypersensitivity to the active substances or to any of the excipients.
PRECAUTIONS
Lamivudine is not recommended for use as monotherapy.
- Renal impairment: In patients with moderate to severe renal impairment, the terminal plasma half-life of Lamivudine is increased due to decreased clearance; therefore the dose should be adjusted.
- Triple nucleoside therapy: There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when Lamivudine was combined with tenofovir disoproxil fumarate and abacavir as well as with tenofovir disoproxil fumarate and didanosine as a once daily regimen.
- Opportunistic infections: Patients receiving Lamivudine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.
- Transmission of HIV: Patients should be advised that current antiretroviral therapy, including Lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions should continue to be taken.
- Pancreatitis: Cases of pancreatitis have occurred rarely. However it is not clear whether these cases were due to the antiretroviral treatment or to the underlying HIV disease. Treatment with Lamivudine should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.
- Lactic acidosis: Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).
Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.
Lactic acidosis generally occurred after a few or several months of treatment. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.
Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.
Patients at increased risk should be followed closely.
- Mitochondrial 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. The main adverse events reported are hematological disorders (anemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behavior). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.
- Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesized. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.
- Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.
- Liver disease: Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events.
If Lamivudine is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of liver function tests and markers of HBV replication is recommended, as withdrawal of Lamivudine may result in an acute exacerbation of hepatitis.
Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.
- Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.
Lamivudine should not be taken with any other medicinal products containing Lamivudine or medicinal products containing emtricitabine.

Ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

PREGNANCY AND LACTATION

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative toxicity. Lamivudine can be used during pregnancy if clinically needed.

For patients co-infected with hepatitis who are being treated with Lamivudine and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of Lamivudine.

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 infants exposed in utero and/or post-natally to nucleoside analogues.

Following oral administration Lamivudine was excreted in breast milk at similar concentrations to those found in serum. Since Lamivudine and the virus pass into breast milk, it is recommended that mothers taking Lamivudine do not breast-feed their infants. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

DRUG INTERACTIONS

Interaction studies have only been performed in adults.

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

- Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40 % increase in Lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of Lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration is warranted, patients should be monitored clinically. Co-administration of Lamivudine with high doses of co-trimoxazole for the treatment of *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis should be avoided.
- The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with Lamivudine. The nucleoside analogues (e.g. didanosine) like zidovudine are not eliminated by this mechanism and are unlikely to interact with Lamivudine.
- A modest increase in C_{max} (28 %) was observed for zidovudine when administered with Lamivudine, however overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of Lamivudine.
- Lamivudine metabolism does not involve CYP3A, making interactions with medicinal products metabolized by this system (e.g. PIs) unlikely.

ADVERSE EFFECTS

The following adverse reactions have been reported during therapy for HIV disease with Lamivudine.

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

- Blood and lymphatic systems disorders: Neutropenia and anemia (both occasionally severe), thrombocytopenia (uncommon); pure red cell aplasia (very rare).
- Nervous system disorders: Headache, insomnia (common); peripheral neuropathy (or paresthesia) (very rare).
- Respiratory, thoracic and mediastinal disorders: Cough, nasal symptoms (common).
- Gastrointestinal disorders: Nausea, vomiting, abdominal pain or cramps, diarrhea (common) pancreatitis, elevations in serum amylase (rare).
- Hepatobiliary disorders: Transient elevations in liver enzymes (uncommon); hepatitis (rare).
- Skin and subcutaneous tissue disorders: Rash, alopecia (common); angioedema (rare).
- Musculoskeletal and connective tissue disorders: Arthralgia, muscle disorders (common); rhabdomyolysis (rare).
- General disorders and administration site conditions: Fatigue, malaise, fever (common).

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

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

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

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term combined antiretroviral exposure (CART). The frequency of which is unknown.

DOSAGE AND ADMINISTRATION

The therapy should be initiated by a physician experienced in the management of HIV infection.

Lamivudine may be administered with or without food.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. The tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

Adults and adolescents (over 12 years of age)

The recommended dose of Lamivudine is 300 mg daily. This may be administered as either 150 mg twice daily or 300 mg once daily.

Patients changing to the once daily regimen should take 150 mg twice a day and switch to 300 mg once a day the following morning. Where an evening once daily regimen is preferred, 150 mg of Lamivudine should be taken on the first morning only, followed by 300 mg in the evening. When changing back to a twice daily regimen patients should complete the days treatment and start 150 mg twice a day the following morning.

Children (under 12 years of age)

Since an accurate dosing can not be achieved with this formulation, dosing according to weight bands is recommended for Lamivudine tablets. This dosing regimen for pediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling, with supporting data from clinical studies.

- For children weighing at least 30 kg: The adult dosage of 150 mg twice daily should be taken.
- For children weighing between 21 kg to 30 kg: The recommended oral dose of Lamivudine is 75 mg taken in the morning and 150 mg taken in the evening.
- For children weighing 14 to 21 kg: The recommended oral dose of Lamivudine is 75 mg taken twice daily.
- Less than three months of age: The limited data available are insufficient to propose specific dosage recommendations.

Renal impairment

Lamivudine concentrations are increased in patients with moderate - severe renal impairment due to decreased clearance. The dose should therefore be adjusted, using oral solution presentation of Lamivudine for patients whose creatinine clearance falls below 30 ml/min.

Dosing recommendations – Adults and adolescents weighing at least 30 kg:

Creatinine clearance (ml/min)	First dose	Maintenance dose
≥50	150 mg	150 mg twice daily
30-<50	150 mg	150 mg once daily
<30	Doses below 150 mg are needed	

There are no data available on the use of Lamivudine in children with renal impairment. Based on the assumption that creatinine clearance and Lamivudine clearance are correlated similarly in children as in adults it is recommended that the dosage in children with renal impairment be reduced according to their creatinine clearance by the same proportion as in adults.

Hepatic impairment

Data obtained in patients with moderate to severe hepatic impairment shows that Lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

OVERDOSAGE

Administration of Lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.

If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Since Lamivudine is dialyzable, continuous hemodialysis could be used in the treatment of overdosage, although this has not been studied.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: June 2015.

This is a medicament

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

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