

DATA SHEET

3TC[®] Oral Solution

Lamivudine oral solution 10mg/mL

Presentation

3TC oral solution contains 10mg/mL lamivudine in a solution containing 20% (w/v) sucrose.

3TC oral solution is a clear, colourless to pale yellow, strawberry and banana flavoured aqueous solution.

Uses

Actions

Pharmacotherapeutic group - nucleoside analogue.

Lamivudine is a potent, selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. It is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine is metabolised intracellularly to the 5'-triphosphate, the active moiety, which has an intra-cellular half-life of 16-19 hours. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependant activities of HIV reverse transcriptase, its main mode of action is as a chain terminator of HIV reverse transcription. Lamivudine has been shown to act additively or synergistically with other anti-HIV agents, particularly zidovudine, inhibiting the replication of HIV in cell culture. Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*. Lamivudine therefore has, *in vitro*, a high therapeutic index.

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine and zalcitabine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according to methodological factors.

In clinical trials, lamivudine in combination with zidovudine has been shown to reduce HIV-1 viral load and to increase CD₄ cell count. Clinical end-point data indicate that lamivudine in combination with zidovudine alone or in combination with zidovudine containing treatment regimens results in a significant reduction in the risk of disease progression and mortality.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received 3TC therapy. Evidence from clinical studies show that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior anti-retroviral therapy.

Lamivudine has been widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (nucleoside reverse transcriptase inhibitors) or different classes (protease inhibitors, non-nucleoside reverse transcriptase inhibitors).

Multiple drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretrovirally-naïve patients as well as in patients presenting with viruses containing the M184V mutations.

The relationship between *in vitro* susceptibility of HIV to lamivudine and the clinical response to therapy remain under investigation.

Pharmacokinetics

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. At therapeutic dose levels i.e. 4mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1-1.9mcg/mL.

Co-administration of lamivudine with food resulted in a delay of t_{max} and a lower C_{max} (decreased by up to 47%). However, the extent (based on the AUC) of lamivudine absorbed was not influenced. No dose adjustment is needed when co-administered with food.

Distribution:- From intravenous studies, the mean volume of distribution is 1.3L/kg and the mean terminal half-life of elimination is 5 to 7 hours. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding to albumin. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean lamivudine CSF/serum concentration ratio 2-4

hours after oral administration was approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Metabolism and elimination:- Lamivudine mean systemic clearance is approximately 0.32L/h/kg, with predominantly renal clearance (>70%) via the organic cationic transport system, and little (<10%) hepatic metabolism. 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). In 60 healthy adult volunteers, 3TC 300mg once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to 3TC 150mg twice daily with respect to intracellular AUC₂₄ and C_{max}. The likelihood of adverse interactions between lamivudine and other medicinal products is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

Renal Impairment:- Lamivudine plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. The dosage should therefore be reduced for patients with a creatinine clearance of <50mL/minute (see Dosage and Administration).

Hepatic impairment:- Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.

Children:- In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age approaching adult values around 12 years of age. Due to these differences, the recommended dose for children from three months to 12 years is 4mg/kg twice a day, which will provide comparable exposure to the adult recommended dose (150mg twice a day).

There are limited pharmacokinetic data for patients less than three months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely to be due to immature renal function and variable absorption. Therefore to achieve similar adult and paediatric exposure, the recommended dose for neonates is 2mg/kg twice a day. However there is no data available in neonates older than one week old.

Elderly:- No pharmacokinetic data are available in patients over 65 years of age.

Pregnancy:- The pharmacokinetics of lamivudine are similar to that of non-pregnant adults. In humans, consistent with passive transmission of lamivudine across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

Indications

3TC in combination with other anti-retroviral agents is indicated for the treatment of HIV infected adults and children.

Dosage and Administration

3TC therapy should be initiated by a physician experienced in the management of HIV infection.

3TC can be taken with or without food.

3TC tablets are also available for patients preferring a tablet formulation.

Adults and adolescents greater than 12 years of age:-

The recommended dose of 3TC is 300mg (30mL) daily. This may be administered as either 150mg (15mL) twice daily or 300mg (30mL) once daily.

Children:-

Less than three months:- The limited data available are insufficient to propose specific dosage recommendations (see Pharmacokinetics).

Three months to twelve years:- The recommended dose is 4mg/kg twice daily up to a maximum of 300mg daily.

Renal Impairment:-

Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance (see Pharmacokinetics). The dosage should therefore be reduced for patients with a creatinine clearance of <50mL/minute as shown in the table below. The same percentage reduction in dose applies for paediatric patients with renal impairment.

Dosing Recommendations – Adult and adolescence >12 years of age:

Creatinine clearance (mL/min)	First Dose	Maintenance Dose
30 to <50	150mg (15mL)	150mg (15mL) once daily
15 to < 30	150mg (15mL)	100mg (10mL) once daily
5 to <15	150mg (15mL)	50mg (5mL) once daily
< 5	50mg (5mL)	25mg (2.5mL) once daily

Dosage Recommendations – Children ≥ 3 months to 12 yrs:

Creatinine clearance (mL/min)	First Dose	Maintenance Dose
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30 to <50	4mg/kg	4mg/kg once daily
15 to < 30	4mg/kg	2.6mg/kg once daily
5 to <15	4mg/kg	1.3mg/kg once daily
< 5	1.3mg/kg	0.7mg/kg once daily

Hepatic impairment:-

No dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment (see Pharmacokinetics).

Elderly:-

No specific data are available, however special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

Contraindications

The use of 3TC is contraindicated in patients with known hypersensitivity to lamivudine or to any ingredient of the preparation.

Warnings and Precautions

3TC is not recommended for use as monotherapy.

Diabetic patients should be advised that an adult dose contains 3g of sucrose.

Patients should be advised that current antiretroviral therapy, including 3TC, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Patients receiving 3TC or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

Renal impairment: Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance. The dose should therefore be adjusted (See Dosage and Administration).

Pancreatitis: Pancreatitis has been observed in some patients receiving 3TC. However it is unclear whether this was due to treatment with the medicinal product or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of 3TC until diagnosis of pancreatitis is excluded.

Lactic acidosis/severe hepatomegaly with steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including lamivudine. A majority of these cases have been in women. Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea). Caution should be exercised when administering 3TC to any patient, and particularly to those with known risk factors for liver disease. Treatment with 3TC should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Fat redistribution: Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and blood glucose levels have been observed either separately or together in some patients receiving combination antiretroviral therapy (see Adverse Effects).

Whilst all members of the PI and NRTI classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicate that there are differences in the risk between individual members of the respective therapeutic classes.

In addition, the lipodystrophy syndrome has a multi-factorial aetiology; with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles.

The long-term consequences of these events are currently unknown.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reconstitution Syndrome: In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* (*P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

Patients co-infected with Hepatitis B virus: Clinical trial and marketed use of 3TC, have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of 3TC, which may have more severe consequences in

patients with decompensated liver disease. If 3TC is discontinued in a patient with HIV and HBV coinfection, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Pregnancy and Lactation

Pregnancy: There is limited data available on the safety of lamivudine in human pregnancy. Studies in humans have confirmed that lamivudine crosses the placenta. Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies (see Preclinical Safety Data) are not always predictive of human response, the findings in the rabbit suggest a potential risk of early embryonic loss.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed in utero or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure in utero or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lactation: Health experts recommend that where possible women infected with HIV do not breast feed their infants in order to avoid the transmission of HIV. Following oral administration lamivudine was excreted in human breast milk at similar concentrations to those found in serum (1-8mcg/mL). Since lamivudine and the virus pass into breast milk it is recommended that mothers taking 3TC do not breast feed their infants.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of 3TC on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of lamivudine. Nevertheless, the clinical status of the patient and the adverse event profile of 3TC should be borne in mind when considering the patient's ability to drive or operate machinery.

Interactions

The likelihood of interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system

e.g. trimethoprim. Other active substances (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

Active substances shown to be predominantly excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.

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

Administration of trimethoprim/sulphamethoxazole 160mg/800mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (See Posology and Method of Administration). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of 3TC with higher doses of co-trimoxazole for the treatment of *Pneumocystis jiroveci* (*P. carinii*) pneumonia and toxoplasmosis has not been studied.

Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. 3TC is therefore not recommended to be used in combination with zalcitabine.

Adverse Effects

The following events have been reported during therapy for HIV disease with 3TC alone and in combination with other anti-retroviral agents. With many it is unclear whether they are related to medicinal products or are as a result of the underlying disease process.

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

Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000) very rare (<1/10,000).

Blood and lymphatic systems disorders

Uncommon: Neutropenia, anaemia, thrombocytopenia.

Very rare: Pure red cell aplasia

Metabolism and nutrition disorders

Common: Hyperlactataemia

Rare: Lactic acidosis (see Warnings and Precautions).

Redistribution/accumulation of body fat (see Warning and Precautions). The incidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.

Nervous system disorders

Common: Headache

Very rare: Paraesthesia. Peripheral neuropathy has been reported although a causal relationship to treatment is uncertain

Gastrointestinal disorders

Common: Nausea, vomiting, upper abdominal pain, diarrhoea

Rare: Pancreatitis, although a causal relationship to treatment is uncertain.

Rises in serum amylase

Hepatobiliary disorders

Uncommon: Transient rises in liver enzymes (AST, ALT)

Skin and subcutaneous tissue disorders

Common: Rash, alopecia

Musculoskeletal and connective tissue disorders

Common: Arthralgia, muscle disorders

Rare: Rhabdomyolysis

General disorders and administration site conditions-

Common: Fatigue, malaise, fever.

Overdosage

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 dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

Pharmaceutical Precautions

Incompatibilities

None reported.

Shelf Life

24 months when stored at or below 25°C.

Discard Oral Solution one month after first opening.

Special Precautions for Storage

Store at or below 30°C.

Medicines Classification

Prescription Medicine.

Package Quantities

Cartons containing 240mL lamivudine 10mg/mL in a white high density polyethylene (HDPE) bottle, with a child-resistant closure. A 10mL oral dosing syringe and an adaptor are also included in the pack.

Further Information

Preclinical Safety Data

Administration of lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. Reductions of erythrocyte and neutrophil counts were identified as the effects most likely to be of clinical relevance.

Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

The results of long term oral carcinogenicity studies with lamivudine in rats and mice did not show any carcinogenic potential.

Reproductive toxicology: Reproductive studies in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. Lamivudine produced small increases in early embryonic loss when administered to pregnant rabbits, at exposure levels comparable to those achieved in man. However, there was no evidence of embryonic loss in rats at exposure levels of approximately 35 times the clinical exposure (based on C_{max}).

List of Excipients

Sucrose (20% w/v), Methyl hydroxybenzoate, Propyl hydroxybenzoate, Citric acid anhydrous, Propylene glycol, Sodium citrate, Artificial banana flavour, Water (purified).

Post-exposure prophylaxis (PEP)

Internationally recognised guidelines (Centre for Disease Control and Prevention - June 1998), recommend that in the event of accidental exposure to HIV infected blood e.g. from a needlestick injury, a combination of Retrovir and 3TC™ should be administered promptly (within one to two hours). In

cases of higher risk of infection a protease inhibitor should be included in the regimen. It is recommended that antiretroviral prophylaxis be continued for four weeks. No controlled clinical studies have been carried out in post-exposure prophylaxis and supporting data is limited. Seroconversion may still occur despite prompt treatment with antiretroviral agents.

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