Teladine®

Tenofovir Disoproxil Fumarate / Lamivudine

FORMS AND PRESENTATION

Teladine®: Tablets: Box of 30.

COMPOSITION

Teladine®: Each tablet contains Tenofovir Disoproxil Fumarate 300mg Eq. to Tenofovir Disoproxil 245mg and Lamivudine 300mg.

Excipients: lactose, starch, croscarmellose sodium, povidone, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, indigo carmine.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Antivirals for systemic use.

ATC code: J05AF07 (Tenofovir Disoproxil) and J05AF05 (Lamivudine).

Tenofovir Disoproxil Fumarate is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir Disoproxil Fumarate requires initial diester hydrolysis for conversion to Tenofovir and subsequent phosphorylations by cellular enzymes to form Tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases alpha and beta, and mitochondrial DNA polymerase gamma.

Lamivudine is a synthetic nucleoside analogue. Intracellularly, Lamivudine is phosphorylated to its active 5'-triphosphate metabolite, Lamivudine Triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of mammalian DNA polymerases alpha and beta, and mitochondrial DNA polymerase-gamma.

Pharmacokinetic properties

Following oral administration of Tenofovir maximum Tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. In vitro binding of Tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01–25 µg/mL. Approximately 70–80% of the intravenous dose of Tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of Tenofovir, the terminal elimination half-life of Tenofovir is approximately 17 hours.

Following oral administration, Lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of Lamivudine 300 mg once daily for 7 days to 60 healthy volunteers, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg/mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hr/mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of Lamivudine is recovered as unchanged drug in the urine. Metabolism of Lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

Effects of Food on Oral Absorption

Teladine® may be administered with or without food.

Administration of Tenofovir following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in Tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of Tenofovir with a light meal did not have a significant effect on the pharmacokinetics of Tenofovir when compared to fasted administration of the drug. Food delays the time to Tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of Tenofovir are 0.33 ± 0.12 µg/mL and 3.32 ± 1.37 µg•hr/mL following multiple doses of Tenofovir 300 mg once daily in the fed state, when meal content was not controlled.

Administration with a high-fat meal in a single-dose bioavailability study resulted in no change in AUC_{last}, AUC, and C_{max} for Lamivudine.

Adults with hepatic impairment

The pharmacokinetics of Tenofovir following a 300 mg dose of Tenofovir have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in Tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients.

The pharmacokinetic properties of Lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for Lamivudine is required for patients with impaired hepatic function. Safety and efficacy of Lamivudine have not been established in the presence of decompensated liver disease.

Adults with renal impairment

The pharmacokinetics of Lamivudine and Tenofovir are altered in patients with renal impairment. Because Lamivudine requires dose adjustment in the presence of renal insufficiency, Teladine® is not recommended for use in patients with creatinine clearance <50 mL/min.

INDICATIONS

Teladine® tablets are indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults.

Additional important information regarding the use of Teladine® for the treatment of HIV-1 infection:

- It is not recommended that Teladine® be used as a component of a triple nucleoside regimen.
- Teladine® should not be co-administered with Lamivudine tablets, Tenofovir Disoproxil Fumarate tablets, or any other Tenofovir and Lamivudine-containing products.
- In treatment experienced patients, the use of Teladine® should be guided by laboratory testing and treatment history.

CONTRAINDICATIONS

Teladine® is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

PRECAUTIONS

- Lactic acidosis/severe hepatomegaly with steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Teladine® tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).
- Patients with HIV-1 and Hepatitis B Virus co-infection: It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. Teladine® tablets are not indicated for the treatment of chronic HBV infection and the safety and efficacy of Lamivudine plus Tenofovir DF have not been established in patients co-infected with HBV and HIV. Due to the risk of development of HIV-1 resistance, Teladine® tablets should only be used in HIV-1 and HBV co-infected patients as part of an appropriate antiretroviral combination regimen. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of Lamivudine or Tenofovir DF. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who are co-infected with HIV and HBV and discontinue Teladine®. If appropriate, initiation of anti-hepatitis B therapy may be warranted.
- Post-treatment exacerbations of hepatitis: Post-treatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with Lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of Lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA.

Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from Lamivudine-containing HIV treatment regimens to non-Lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of Lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of Lamivudine alters the course of post-treatment exacerbations of hepatitis.

- Use with interferon- and ribavirin- based regimens: In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as Lamivudine, a component of Teladine®. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with Lamivudine in HIV/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and Teladine® should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of Teladine® should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6).
- New onset or worsening renal impairment: Tenofovir and is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of Tenofovir Disoproxil Fumarate.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with Teladine®. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.

Teladine® should be avoided with concurrent or recent use of a nephrotoxic agent.

- Decreases in bone mineral density: Bone mineral density monitoring should be considered for HIV-1 infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of Tenofovir Disoproxil Fumarate.

- Fat redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.
- Immune reconstitution syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including Lamivudine and Tenofovir. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an

inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

- Early virologic failure: Clinical studies in HIV-infected patients have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV- 1 protease inhibitor. In particular, there have been reports of a high rate of virological failure and of emergence of resistance at early stage in HIV patients when Tenofovir Disoproxil Fumarate was combined with Lamivudine and abacavir as well as with Lamivudine and didanosine as a once daily regimen.
- Co-administration with Related Products: Teladine® is a fixed-dose combination tablet of Lamivudine and Tenofovir Disoproxil Fumarate, Teladine® should not be co-administered with other drugs containing Lamivudine or Tenofovir Disoproxil Fumarate. Due to similarities between emtricitabine and Lamivudine, Teladine® should not be co-administered also with emtricitabine containing products.

PREGNANCY AND LACTATION

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to Tenofovir. There are, however, no adequate and well-controlled studies in pregnant women.

Lamivudine pharmacokinetics in the pregnant women were similar to those obtained following birth and in non-pregnant adults. Lamivudine concentrations were generally similar in maternal, neonatal, and cord serum samples. In a subset of subjects from whom amniotic fluid specimens were obtained following natural rupture of membranes, amniotic fluid concentrations of Lamivudine ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily) and were typically greater than 2 times the maternal serum levels. Because animal reproduction studies are not always predictive of human response, Teladine® tablets should be used during pregnancy only if clearly needed.

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1.Studies in rats have demonstrated that Tenofovir and Lamivudine are secreted in milk. It is not known whether Tenofovir is excreted in human milk. Lamivudine is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving Teladine®.

DRUG INTERACTIONS

No drug interaction studies have been conducted using Teladine® tablets. Drug interaction studies have been conducted with Lamivudine and Tenofovir Disoproxil Fumarate, the components of Teladine®.

Tenofovir

Co-administration of Teladine® and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When Tenofovir Disoproxil Fumarate was administered with didanosine the Cmax and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving Tenofovir DF with didanosine 400 mg daily.

In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is co-administered with Teladine®. Data are not available to recommend dose adjustment of didanosine for patients weighing <60 kg. When coadministered, Teladine® and didanosine enteric coated capsule may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with Teladine® should be under fasted conditions.

Atazanavir has been shown to increase Tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and Teladine® should be monitored for Tenofovir-associated adverse reactions. Teladine® should be discontinued in patients who develop Tenofovir –associated adverse reactions.

Tenofovir decreases the AUC and C_{min} of atazanavir. When co-administered with Teladine®, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be co-administered with Teladine®.

Lopinavir/ritonavir has been shown to increase Tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and Teladine® should be monitored for Tenofovir-associated adverse reactions. Teladine® should be discontinued in patients who develop Tenofovir-associated adverse reactions.

Since Tenofovir is primarily eliminated by the kidneys, co-administration of Teladine® with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of Tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may increase concentrations of Lamivudine and/or Tenofovir.

Lamivudine

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs 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).

Trimethoprim 160 mg and sulfamethoxazole 800 mg (TMP/SMX) once daily has been shown to increase Lamivudine exposure (AUC) by 43%. No change in dose of either drug is recommended. There is no information regarding the effect on Lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of Lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of Lamivudine in combination with zalcitabine is not recommended.

ADVERSE EFFECTS

Tenofovir

- Immune system disorders: Allergic reaction.
- Metabolism and nutrition disorders: Hypophosphatemia, lactic acidosis, hypokalemia.
- Respiratory, thoracic, and mediastinal disorders: Dyspnea.
- Gastrointestinal disorders: Abdominal pain, pancreatitis, increased amylase.
- Renal and urinary disorders: Renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus, polyuria, interstitial nephritis (including acute cases).
- Hepatobiliary disorders: Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT).
- Skin and subcutaneous tissue disorders: Rash.
- Musculoskeletal and connective tissue disorders: Rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy.
- General disorders and administration site conditions: Asthenia.

Lamivudine

- Body as a whole: Redistribution/accumulation of body fat.
- Digestive: Stomatitis.
- Endocrine and metabolic: Hyperglycemia.
- General: Weakness.
- Hemic and lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, and splenomegaly.
- Hepatic and pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, post-treatment exacerbation of hepatitis B.
- Hypersensitivity: Anaphylaxis, urticaria.
- Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
- Skin: Alopecia, rash, pruritus.

DOSAGE AND ADMINISTRATION

The dose of Teladine® is one tablet once daily taken orally with or without food.

Dose adjustment for renal impairment

Dose adjustment is necessary for patients with creatinine clearance <50mL/min. Because it is a fixed-dose tablet, Teladine® cannot be prescribed for these patients.

No dose adjustment is necessary for patients with creatinine clearance >50mL/min. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed for these patients.

The pharmacokinetics of Tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients.

OVERDOSAGE

Tenofovir

Limited clinical experience at doses higher than the therapeutic dose of Tenofovir 300 mg is available. In Study 901, 600 mg Tenofovir Disoproxil Fumarate was administered to 8 patients orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known. If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of Tenofovir, a four-hour hemodialysis session removed approximately 10% of the administered Tenofovir dose.

Lamivudine

There is no known antidote for Lamivudine. One case of an adult ingesting 6 g of Lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose have been reported. One case was a single dose of 7 mg/kg of Lamivudine; the second case involved use of 5 mg/kg of Lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of Lamivudine was removed via 4-hour hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a Lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

Date of revision: May 2013.

This is a medicament

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

Council of Arab Health Ministers
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