For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Tenolon 300mg Film Coated Tablet

Tenofovir Disoproxil Fumarate

300 mg Film-Coated Tablet
Antiviral (Nucleoside and Nucleotide Reverse Transcriptase Inhibitor)

WARNINGS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including Tenofovir disoproxil fumarate in combination with other antiretrovirals (see warning and precautions). Severe acute exacerbations of hepatitis have been reported in hepatitis B virus (HBV)-infected patients who have discontinued anti-hepatitis B therapy, including Tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including Tenofovir disoproxil fumarate if appropriate, resumption of anti-hepatitis B therapy may be warranted (see warning and precautions).

Composition
Each film coated tablet contains:

Tenofovir Disoproxil Fumarate	300mg
Equivalent to Tenofovir Disoproxil	245mg

Description
Blue, almond-shaped, film coated tablets with white cores, and debossed with "LZ30" on one side and with "300" on the other side.

Pharmacology

Pharmacodynamics

In vivo, tenofovir DF is hydrolysed to tenofovir, which is then phosphorylated by cellular kinases to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV reverse transcriptase by competing with the nucleotide deoxyadenosine 5′- triphosphate for incorporation into viral DNA. Once incorporated into viral DNA, it terminates DNA elongation because of lack of a ribose ring**.**

Pharmacokinetics

Absorption and Distribution
The oral bioavailability of tenofovir after administration of tenofovir DF 300 mg/day was 25% and increased to 39% when tenofovir DF was administered with a standardised high fat meal. Median steady-state maximum serum tenofovir concentrations (Cmax) and the area under the serum tenofovir concentration-time curve (AUC) were 326 ng/mL and 3020 ng • h/mL in patients infected with HIV who received tenofovir DF 300 mg/day with food for 28 days. The median time to Cmax was 2.3 hours.

Metabolism and Elimination
Tenofovir concentrations in serum decline in a biphasic manner. Administration of Tenofovir DF 300mg/day with food for 28 days to patients with HIV infection resulted in a median serum terminal elimination half-life for tenofovir of 14.4 hours and clearance rate of 0.51 L/h/kg. In an in vitro study, the half-life of tenofovir diphosphate in activated Peripheral blood mononuclear cells (PBMCs) preincubated with tenofovir DF or tenofovir was 11 hours; however, the half-life of tenofovir diphosphate in resting PBMC preincubated with tenofovir was 49 hours.

Indications HIV-1 infection
Tenolon 300mg Film Coated Tablet is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.
The following points should be considered while initiating therapy with Tenolon 300mg Film Coated Tablet for the treatment of HIV-1 infection:

- Tenolon 300mg Film Coated Tablet should not be used in combination with TRUVADA or ATRIPLA

Chronic Hepatitis B
Tenolon 300mg Film Coated Tablet is indicated for the treatment of chronic hepatitis B in adults.
The following points should be considered when initiating therapy with Tenolon 300mg Film Coated Tablet for the treatment of HBV infection:

- This indication is based primary on data from treatment of subjects who were nucleoside-treatment- naïve and a smaller number of subjects who had previously received lamivudine or adefovir dipivoxil. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis with compensated liver disease.
- Tenolon 300mg Film Coated Tablet was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease.
- The numbers of subjects in clinical trials who had lamivudine- or adefovir- associated substitutions at baseline were too small to reach conclusions of efficacy

Dosage and administration
Recommended Dose in adults
For the treatment of HIV-1 or chronic hepatitis B: The dose is one 300 mg Tenolon 300mg Film Coated Tablet tablet once daily taken orally, without regard to food.

In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown.

Dose Adjustment for Renal Impairment in Adults
Significantly increased drug exposures occurred when Tenolon 300mg Film Coated Tablet was administered to subjects with moderate to severe renal impairment. Therefore, the dosing interval of Tenolon 300mg Film Coated Tablet should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modelling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients.

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment.

Table 1 Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]			**Hemodialysis Patients**
	≥ 50	30-49	10-29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

a. Calculated using ideal (lean) body weight
b. Generally, once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration.

Tenolon 300mg Film Coated Tablet should be administered following completion of dialysis.
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.

No data are available to make dose recommendations in pediatric patients 12 years of age and older with renal impairment.

Contraindications
Hypersensitivity to the active substance or to any of the excipients in this product.

Warning and Precautions

Lactic Acidosis/Severe Hepatomegaly with Steatosis.

Lactic acidosis and severe hepatomegaly with steatosis (sometimes fatal) have been reported rarely in patients receiving nucleoside reverse transcriptase inhibitors (NRTIs) alone or in conjunction with other antiretroviral agents.

Caution should be observed when nucleoside analogs are used in patients with known risk factors for liver disease; however, lactic acidosis and severe hepatomegaly with steatosis have been reported in patients with no known risk factors. Tenofovir therapy should be interrupted in any patient with clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (signs of hepatotoxicity include hepatomegaly and steatosis even in the absence of marked increases in serum aminotransferase concentrations).

Patients Co-infected with HIV and HBV

The need to avoid antiviral resistance complicates the selection of active agents. Resistance to HIV therapy limits the choices for treatment of HBV infection. Tenofovir may select for resistance mutations in HIV polymerase and hence tenofovir should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen.

HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with tenofovir. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with tenofovir.

Renal Impairment
Although tenofovir did not show any significant cytotoxicity in isolated human RPTECs in an in vitro study, tenofovir has been associated with changes in renal function in vivo. Changes in renal function (incidence of hypophosphataemia and elevations in serum creatinine) in antiretroviral-naive patients were similar for those receiving tenofovir DF- or stavudine-based therapy after 96 weeks. However, rare episodes of acute renal failure have been observed in patients receiving tenofovir DF in combination with other with antiretroviral drugs.
Additional safety recommendations include the following: i) the dosing interval of tenofovir DF should be adjusted in patients with baseline Clcr, < 50 ml/min; ii) the safety and effectiveness of these dosing interval adjustment recommendations have not been evaluated clinically, therefore, clinical response to treatment and renal function should be closely monitored in these patients; iii) tenofovir DF should be avoided with concurrent or recent use of nephrotoxic agents; and iv) patients at risk for, or with a history of renal dysfunction, and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in Cr and phosphorus.
The possibility of nephrotoxicity with tenofovir DF primarily because of the proximal renal tubular dysfunction (Fanconi's syndrome) observed in patients treated with another NtRI adefovir dipivoxil, when it was given at doses of 60 or 120 mg/day in clinical trials to treat HIV infection. Fortunately, none of the tenofovir DF trials has shown evidence of nephrotoxicity with tenofovir DF in patients with normal renal function. However, there have now been several reports of proximal renal tubular dysfunction and or hypophosphatemia in patients taking tenofovir DF.

Decreases in Bone Mineral Density
In reference to a published trial report decreases in bone mineral density at the lumbar spine, increases in levels of 4 biochemical markers of bone metabolism, and increased serum parathyroid hormone levels were reported in HIV-infected patients receiving tenofovir concomitantly with lamivudine and efavirenz; these effects also were reported to a lesser extent in patients who received a regimen of stavudine, lamivudine, and efavirenz. With the exception of bone-specific alkaline phosphatase concentrations, these changes generally remained within the normal range and the clinical importance is unknown. There were 4 bone fractures reported in patients receiving the regimen that contained tenofovir and 6 reported in those receiving the regimen that did not include tenofovir.

Bone monitoring should be considered for HIV-infected patients who have a history of pathologic bone fracture or are at substantial 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, appropriate consultation should be obtained.Osteomalacia and decreases in bone mineral density have been reported in toxicology studies in juvenile animals given high doses of tenofovir.

Fat Redistribution
In HIV-infected patients, 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 combination 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 tenofovir disoproxil fumarate. 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 like tenofovir,abacavir and lamivudine result in an unexpected and unacceptably high rate of nonresponse and incidence of K65R and M184V/I and hence this 3 drug regimen should not be used. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Drug Interactions
Notable drug interactions occur when tenofovir DF is administered with didanosine or atazanavir. Otherwise, tenofovir DF can be administered with all other antiretrovirals without dose adjustments. Furthermore, there are no relevant pharmacokinetic interactions with methadone, oral contraceptives, ribavirin, or rifampacin.

Tenofovir DF and didanosine

Administration of tenofovir DF with ddI is not recommended. This combination increases exposure to ddI by 40 - 60%. which may increase the risk of ddI-related adverse events. In addition, administration of tenofovir DF with ddI 400 mg daily has been associated with significant CD4 cell decreases, possibly due to an intracellular interaction that increases phosphorylated (i.e., active) ddI. Rare cases of pancreatitis and lactic acidosis have also been reported.

Tenofovir DF and atazanavir
Once daily administration of atazanavir (400 mg) with tenofovir results in decreased atazanavir area under the curve (AUC) and trough levels (Cmin by 25 and 40%, respectively. When ritonavir was added to atazanavir, the negative impact of tenofovir on atazanavir Cmin was significantly reduced, whereas the decrease in AUC was of the same magnitude (decrease of 25 and 26% of AUC and Cmin,, respectively, compared with atazanavir/ritonavir 3001100 mg). However, this does not seem to be clinically relevant in terms of the antiviral activity of this combination The mechanism for this drug-drug interaction remains unknown The current recommendation for administration of atazanavir with tenofovir is to use atazanavir 300 mg and ritonavir 100 mg, both once daily. The administration of atazanavir/ritonavir with tenofovir resulted in increased exposure to tenofovir by Cmin, C, and AUC. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.

Nucleoside combinations
One study tested once-daily nudeosides lamivudine (3TC) and abacavir in combination with either tenofovir DF or efavirenz (EFV). The unfavourable result of this investigation was a high rate of resistance mutations after 12 weeks in the tenofovir arm with high rates of key mutations for 3TC (98% at position M184 in reverse transcriptase gene) and tenofovir (54% at position K65). The mechanism of this drug-drug interaction was presumed to be due to an unfavourable synergistic selection pressure from all three agents in the tenofovir arm toward two point mutations, M184V and K65R. Both abacavir and tenofovir DF select for the K65R mutation, which reduces susceptibility to both drugs, as well as to 3TC.Another trial evaluating two once-daily reverse transcriptase inhibitor combinations, that is ddI and EFV plus either tenofovir DF or 3TC, as initial therapy in 340 patients showed inferiority of the tenofovir DF and ddI1EFV combination, with an unexpected high rate of early virological failure, especially in patients with high viral load (> 100,000 copies/ml) and low (< 200) CD4 cells.10These two studies resulted in avoidance of once-daily regimens that include the unfavourable nudeoside combinations of tenofovir DF plus abacavir or ddI for initial antiretroviral therapy.

Patients with Impaired Renal Function
It is recommended that the dosing interval for tenofovir DF be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis.

Pregnancy
Pregnancy category B
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. Because animal reproduction studies are not always predictive of human response, tenofovir should be used during pregnancy only if clearly needed.

Lactation
It is not known whether tenofovir is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown. The Centers for Disease Control and Prevention recommend that women infected with HIV not breastfeed their infants in order to avoid postnatal spread of the virus through breast milk.

Pediatric Use
Safety and efficacy in pediatric patients have not been established and there is no recommended dose for children.

Undesirable Effects
Tenofovir DF has a limited effect on mitochondrial DNA polymerase.
The most common treatment-related adverse events are predominantly gastrointestinal nature and include: diarrhoea, headache, vomiting, flatulence, abdominal pain and anorexia.

Observed During Clinical Practice:
Tenofovir DF has been associated with pancreatitis, hypophosphataemia, lactic acidosis, dizziness, dyspnoea, rash, renal insufficiency, kidney failure and Fanconi syndrome during postmarketing surveillance. Concomitant administration of tenofovir disoproxil fumarate and didanosine in a patient with renal insufficiency may have resulted in accumulation of both drugs, contributing to acute renal failure and severe lactic acidosis. Renal insufficiency, renal failure, Fanconi syndrome, proteinuria, increased serum creatinine, acute tubular necrosis, and proximal tubulopathy have been reported via post marketing experience with tenofovir therapy.

Overdosage
Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In reference to a published trial report, 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 disoproxil fumarate, a 4 -hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

Storage
Preserve in tightly closed container, store not above 30°C at dry place.

Packing/Pack size
HDPE bottle of 30 Tablets.

Mfg By
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