Tenvir

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Tenvir

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

Tenvir

(Tenofovir Disoproxil Fumarate Tablets 300 mg)

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 WARNINGS 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 WARNINGS AND PRECAUTIONS).

Composition
Each film coated tablet contains
Tenofovir Disoproxil Fumarate……300 mg
Equivalent to Tenofovir Disoproxil…..245 mg
Colour: Lake Indigo carmine and Titanium dioxide

Description
Light blue coloured, capsule shaped, biconvex film coated tablets with 'TNV' debossed on one side and plain 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
TENVIR 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 TENVIR for the treatment of HIV-1 infection:
- TENVIR should not be used in combination with TRUVADA or ATRIPLA

Chronic Hepatitis B
TENVIR is indicated for the treatment of chronic hepatitis B in adults.
The following points should be considered when initiating therapy with TENVIR 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.
- TENVIR 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 TENVIR 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 TENVIR was administered to subjects with moderate to severe renal impairment. Therefore, the dosing interval of TENVIR 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.

TENVIR 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
None

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.

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PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Tenvir 300 mg film-coated tablets
(Tenofovir Disoproxil Fumarate Tablets 300 mg)
Each film coated tablet contains
Tenofovir Disoproxil Fumarate……300 mg
Equivalent to Tenofovir Disoproxil…..245 mg
Colour: Lake Indigo Carmine & Titanium Dioxide

The other ingredients are:
Lactose monohydrate NF
Croscarmellose sodium NF
Polysorbate 80 NF
Corn Starch NF
Microcrystalline cellulose NF
Magnesium stearate NF
Opadry II Y-30-10671-A-Light blue Inhouse Specification

1 WHAT TENVIR IS AND WHAT IT IS USED FOR
TENVIR (tenofovir) is a treatment for Human Immunodeficiency Virus (HIV) infection in adults and pediatric patients 12 years of age and older.

Tenofovir is also used to treat chronic hepatitis B, an infection with hepatitis B virus (HBV), in adults.

You do not have to have HIV to be treated with tenofovir for HBV. **TENVIR** contains the active substance *tenofovir disoproxil*. This active substance is an *antiretroviral* or *antiviral* medicine which is used to treat HIV or HBV or both. Tenofovir is a *nucleotide reverse transcriptase inhibitor*, generally known as an NRTI and works by interfering with the normal working of enzymes (in HIV: *reverse transcriptase*; in hepatitis B: *DNA polymerase*) that are essential for the viruses to reproduce themselves. In HIV **TENVIR** should always be used combined with other medicines to treat HIV infection. **This medicine is not a cure for HIV infection.** While taking **TENVIR** you may still develop infections or other illnesses associated with HIV infection. You can also pass on HIV or HBV to others, so it is important to take precautions to avoid infecting other people.

2 BEFORE YOU TAKE TENVIR
Do not take TENVIR:
- If you are hypersensitive (allergic) to tenofovir disoproxil fumarate or any of the other ingredients of **Tenvir** tablets.

If this applies to you, tell your doctor immediately and don't take TENVIR.

Take special care with TENVIR:
- **Tell your doctor if you have had kidney disease or if tests have shown problems with your kidneys. TENVIR** may affect your kidneys. Before starting treatment, your doctor may order blood tests to check your kidney function and may advise you to take the tablets less often. Your doctor may also order blood tests during treatment to monitor your kidneys.

TENVIR is not usually taken with other medicines that can damage your kidneys (see *Taking other medicines*). If this is unavoidable, your doctor will monitor your kidney function once a week.
- **Talk to your doctor if you are over 65.** Tenofovir has not been studied in patients over 65 years of age. If you are older than this and are prescribed **TENVIR**, your doctor will monitor you carefully.
- **Do not give TENVIR to children and adolescents** under 18 years of age.
- **Talk to your doctor if you have a history of liver disease, including hepatitis.** Patients with liver disease including chronic hepatitis B or C, who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications. If you have hepatitis B infection, your doctor will carefully consider the best treatment for you. If you have a history of liver disease or chronic hepatitis B infection your doctor may conduct blood tests to monitor your liver function.

Look out for possible signs of lactic acidosis (excess of lactic acid in your blood) once you start taking **TENVIR**. Possible signs of lactic acidosis are:
  - **deep, rapid breathing**
  - **drowsiness**
  - **nausea, vomiting and stomach pain**
- This rare but serious side effect can cause enlargement of the liver and has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if they are very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with **TENVIR**, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.
- **Take care not to infect other people. TENVIR** does not reduce the risk of passing on HIV or HBV to others through sexual contact or blood contamination. You must continue to take precautions to avoid this.

Other precautions
In the treatment of HIV, combination antiretroviral therapies (including tenofovir) may raise blood sugar, increase blood fats (hyperlipaemia), cause changes to body fat, and resistance to insulin (see section 4, *Possible side effects*).

If you are diabetic, overweight or have high cholesterol, talk to your doctor.

Look out for infections. If you have advanced HIV infection (AIDS) and have an infection, you may develop symptoms of infection and inflammation or worsening of the symptoms of an existing infection once treatment with **TENVIR** is started. These symptoms may indicate that your body's improved immune system is fighting infection. Look out for signs of inflammation or infection soon after you start taking **TENVIR**. If you notice signs of inflammation or infection, **tell your doctor at once.**

Bone problems Some patients with HIV taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms tell your doctor.

Taking other medicines
Do not take TENVIR if you are already taking other medicines containing tenofovir disoproxil fumarate. Do not take **TENVIR** and adefovir dipivoxil at the same time.
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- **It is very important to tell your doctor if you are taking other medicines that may damage your kidneys.**

These include:
- aminoglycosides, pentamidine or vancomycin (for bacterial infection)
- amphotericin B (for fungal infection)
- foscarnet, ganciclovir, or cidofovir (for viral infection)
- interleukin-2 (to treat cancer)
- adefovir dipivoxil (for HBV)
- tacrolimus (for suppression of the immune system)
- **Other medicines containing didanosine (for HIV infection):** Taking **TENVIR** with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood and may reduce CD4 cell counts. Rarely, inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes caused death, have been reported when medicines containing tenofovir disoproxil fumarate and didanosine were taken together. Your doctor will carefully consider whether to treat you with combinations of tenofovir and didanosine.
- **Don't stop any anti-HIV medicines** prescribed by your doctor when you start **TENVIR** if you have both HBV and HIV.

Taking TENVIR with food and drink
- **Take TENVIR with food** (for example, a meal or a snack).

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
- **You must not take TENVIR during pregnancy** unless specifically discussed with your doctor. There are no clinical data on the use of **TENVIR** in pregnant women and it is not usually used unless absolutely

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SAP Code: xxxxxxxx (Ver. 01)
Leaflet size: 205 x 300 mm
Size after folding: 41 x 37 mm
Colour:
Black

Reference / Supersedes: 21065654
Country : Malaysia
Date: 21-06-2024

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necessary.
- **Try to avoid getting pregnant** during treatment with **TENVIR**. You must use an effective method of contraception to avoid becoming pregnant.
- **If you become pregnant,** or plan to become pregnant, ask your doctor about the potential benefits and risks of your antiretroviral therapy to you and your child.
- **If you have taken TENVIR** during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took medicines like tenofovir (NRTIs) during pregnancy, the benefit from the protection against the virus outweighed the risk of side effects.
- **Do not breast-feed during treatment with TENVIR.** It is not yet known whether the active substance in this medicine passes into human breast milk.
- If you are a woman with HIV or HBV do not breast-feed, to avoid passing the virus to the baby in breast milk.

Driving and using machines
TENVIR can cause dizziness. If you feel dizzy while taking **TENVIR**, **do not drive** and do not use any tools or machines.

3 HOW TO TAKE TENVIR
- **Always take TENVIR exactly as your doctor has told you**. You should check with your doctor or pharmacist if you are not sure.

The usual dose:
- The recommended dose is:
- **Adults: 1 tablet each day with food** (for example, a meal or a snack).
- **Adolescents aged 12 to less than 18 years who weigh at least 35 kg**: 1 tablet each day with food (for example, a meal or a snack).
- **Always take the dose recommended by your doctor.** This is to make sure that your medicine is fully effective, and to reduce the risk of developing resistance to the treatment. Do not change the dose unless your doctor tells you to.
- **If you are an adult and have problems with your kidneys**, your doctor may advise you to take TENVIR less frequently.
- If you have HBV your doctor may offer you an HIV test to see if you have both HBV and HIV.

Please refer to the patient information leaflets of the other antiretrovirals for guidance on how to take those medicines.

If you forget to take TENVIR.
It is important not to miss a dose of **TENVIR.**

If you miss a dose of **TENVIR,** take it as soon as you can, and then take your next dose at its regular time.

If it is almost time for your next dose anyway, forget about the missed dose. Wait and take the next dose at the regular time. Do not take a double dose to make up for a forgotten tablet.

If you throw up less than 1 hour after taking TENVIR, take another tablet. You do not need to take another tablet if you were sick more than 1 hour after taking **TENVIR**.

If you stop taking TENVIR
- Don't stop taking **TENVIR** without your doctor's advice. Stopping treatment with **TENVIR** may reduce the effectiveness of the treatment recommended by your doctor. Talk to your doctor before you stop taking **TENVIR** for any reason, particularly if you are experiencing any side effects or you have another illness. Contact your doctor before you restart taking **TENVIR** tablets.
- **If you have hepatitis B or HIV and hepatitis B together (co-infection),** it is very important not to stop your tenofovir treatment without talking to your doctor first. Some patients have had blood tests or symptoms indicating that their hepatitis has got worse after stopping tenofovir. You may require blood tests for several months after stopping treatment.

Tell your doctor immediately about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, **TENVIR** can cause side effects, although not everybody gets them.
Very common side effects
(These can affect at least 10 in every 100 patients)
- diarrhoea, being sick (vomiting), feeling sick (nausea), dizziness

Tests may also show:
- decreases in phosphate in the blood

Common side effects
(These can affect up to 10 in every 100 patients)
- headache, stomach pain, feeling tired, feeling bloated, flatulence

Rare side effects
(These can affect up to 1 in every 1,000 patients)
- excess lactic acid in the blood (lactic acidosis, a serious side effect that can be fatal). The following side effects may be signs of lactic acidosis:
  - deep rapid breathing
  - drowsiness
  - feeling sick (nausea), being sick (vomiting) and stomach pain

If you think you may have lactic acidosis, contact your doctor immediately.
- pain in the tummy (abdomen) caused by inflammation of the pancreas
- changes to your urine and back pain caused by kidney problems, including kidney failure
- rash

Tests may also show:
- increased creatinine in your blood
- liver and pancreas problems

Very rare side effects
(These can affect less than 1 in every 10,000 patients)
- shortness of breath
- pain in the tummy (abdomen) caused by inflammation of the liver
- feeling weak

Tests may also show:
- damage to kidney tubule cells

Other possible effects
You may also experience muscle pain or weakness and softening of the bones (both associated with kidney problems), inflammation of the kidney, passing a lot of urine and feeling thirsty.
In the treatment of HIV, combination antiretroviral therapy (including tenofovir) may change your body shape, by changing the way body fat is distributed. You may lose fat from your legs, arms and face; gain fat around the tummy (abdomen) and internal organs; get larger breasts or fatty lumps on the back of the neck ('buffalo hump'). The cause and the long-term effects of these changes are not yet known.
In the treatment of HIV, combination antiretroviral therapy may also cause increased fats in the blood (hyperlipaemia) and resistance to insulin. Your doctor will test for these changes. **If any of the side effects get serious,** or if you notice any side effects not listed in this leaflet, **please tell your doctor.**

5. STORING TENVIR
Keep out of the reach and sight of children.
Store below 30° C
Do not use after the expiry date stated on the bottle and carton.

6. OVERDOSE
If you accidentally take too many **TENVIR** tablets, contact your doctor or nearest emergency department for advice. Keep the tablet bottle with you so that you can easily describe what you have taken

7.FURTHER INFORMATION
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

Marketing Authorisation holder in Malaysia
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Mfd. by Cipla Ltd.
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L-138, L-147, L-147/1 to L-147/3 & L-147/A
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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 [8], 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
Store below 30˚C

Shelf life
24 months.

Packing/Pack size
Container of 30 Tablets.

Registration holder in Malaysia
CIPLA MALAYSIA SDN BHD
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Amcorp Trade Centre, 18 Persiaran Barat,
46 050 Petaling Jaya, Selangor, Malaysia

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Plot No. S-103 to S-105, S-107 to S-112,
L-138, L-147, L-147/1 to L-147/3 & L-147/A
Verna Industrial Estate,Verna, Goa India

DATE OF REVISION OF THE TEXT
June 2024

List of References

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