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Tenofovir Disoproxil Fumarate

VIHOF13-0 (PHIL)

Hofovir

300 mg Film-Coated Tablets
Direct Acting Antiviral
(Nucleoside and Nucleotide Reverse Transcriptase Inhibitor)

DESCRIPTION
A film-coated tablet which the white core appears when coating removed.

COMPOSITION
Each film coated tablet consists of tenofovir disoproxil fumarate 300mg equivalent to tenofovir disoproxil 245mg.

ACTIONS AND PHARMACOLOGY
Tenofovir Disoproxil Fumarate belongs to drug class antiviral for systemic use or nucleoside and nucleotide reverse transcriptase inhibitors.

Tenofovir disoproxil fumarate is the fumarate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits HIV-1 reverse transcriptase and the HBV polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ. At concentrations of up to 300 µmol/l, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in *in vitro assays*.

PHARMACOKINETICS
Tenofovir disoproxil is a water soluble ester prodrug which is rapidly converted *in vivo* to tenofovir and formaldehyde. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.

Absorption
Following oral administration of tenofovir disoproxil to HIV infected patients, tenofovir disoproxil is rapidly absorbed and converted to tenofovir. Administration of tenofovir disoproxil with a light meal did not have a significant effect on the pharmacokinetics of tenofovir.

Distribution
After oral administration of tenofovir disoproxil, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents.

Elimination
Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration.

INDICATION
- For the treatment of HIV-1 infection in combination with other antiretroviral medicinal products for adults
- For the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.
- For the treatment of chronic hepatitis B in adults with:
  - compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis
  - evidence of lamivudine-resistant hepatitis B virus
  - decompensated liver disease
- For the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age with compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients in Tenofovir disoproxil fumarate (Hofovir).

WARNING AND PRECAUTIONS
General
HIV antibody testing should be offered to all HBV infected patients before initiating tenofovir disoproxil therapy.

HIV-1
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Chronic hepatitis B
Patients must be advised that tenofovir disoproxil has not been proven to prevent the risk of transmission of HBV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

Triple therapy with nucleosides/nucleotides
There have been reports of a high rate of virological failure and of emergence of resistance at an early stage in HIV patients when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once-daily regimen.

Renal and bone effects in adult population
Renal effects
Tenofovir is principally eliminated via the kidney. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil in clinical practice.

Renal monitoring
It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with tenofovir disoproxil and renal function (creatinine clearance and serum phosphate) is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients at risk for renal impairment, a more frequent monitoring of renal function is required.

Renal management
If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any adult patient receiving tenofovir disoproxil, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should also be given to interrupting treatment with tenofovir disoproxil in adult patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l). Interrupting treatment with tenofovir disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

Co-administration and risk of renal toxicity
Use of tenofovir disoproxil should be avoided with concurrent or recent use of a nephrotoxic medicinal product (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil and nephrotoxic agents is unavoidable, renal function should be monitored weekly. Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If tenofovir disoproxil is co-administered with an NSAID, renal function should be monitored adequately. A higher risk of renal impairment has been reported in patients receiving tenofovir disoproxil in combination with a ritonavir or cobicistat boosted protease inhibitor. A close monitoring of renal function is required in these patients. In patients with renal risk factors, the co-administration of tenofovir disoproxil with a boosted protease inhibitor should be carefully evaluated. Tenofovir disoproxil has not been clinically evaluated in patients receiving medicinal products which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g. cidofovir, a known nephrotoxic medicinal product). These renal transport proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir. Consequently, the pharmacokinetics of these medicinal products, which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4, might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicinal products which are secreted by the same renal pathway is not recommended, but if such use is unavoidable, renal function should be monitored weekly.

Renal impairment
Renal safety with tenofovir disoproxil has only been studied to a very limited degree in adult patients with impaired renal function (creatinine clearance < 80 ml/min).

Adult patients with creatinine clearance < 50 ml/min, including haemodialysis patients
There are limited data on the safety and efficacy of tenofovir disoproxil in patients with impaired renal function. Therefore, tenofovir disoproxil should only be used if the potential benefits of treatment are considered to outweigh the potential risks. In patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis use of tenofovir disoproxil is not recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored.

Bone effects
Use of tenofovir disoproxil fumarate may be associated with a decrease in bone mineral density.Alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures. Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected or detected then appropriate consultation should be obtained.

Renal and bone effects in paediatric population
There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.

Renal effects
Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to < 12 years.

Renal monitoring
Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment, and monitored during treatment as in adults.

Renal management
If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of tenofovir disoproxil treatment. Interrupting treatment with tenofovir disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

Co-administration and risk of renal toxicity
The same recommendations apply as in adults.

Renal impairment
The use of tenofovir disoproxil is not recommended in paediatric patients with renal impairment.

Tenofovir disoproxil should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during tenofovir disoproxil therapy.

Bone effects
Tenofovir disoproxil fumarate may cause a reduction in BMD. The effects of tenofovir disoproxil-associated changes in BMD on long-term bone health and future fracture risk are currently unknown.

If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.

Patients with HIV and hepatitis B or C virus co-infection
Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

Discontinuation of Hofovir therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Hofovir should be closely monitored with both clinical and laboratory follow-up for at least 6 months after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Liver disease
Safety and efficacy data are very limited in liver transplant patients. There are limited data on the safety and efficacy of tenofovir disoproxil in HBV infected patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

Exacerbations of hepatitis
Flares on treatment: Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Flares after treatment discontinuation: Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. Hepatic function should be

monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Co-infection with hepatitis C or D: There are no data on the efficacy of tenofovir in patients co-infected with hepatitis C or D virus.

Co-infection with HIV-1 and hepatitis B: Due to the risk of development of HIV resistance, tenofovir disoproxil should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients. Patients with preexisting liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered. However, it should be noted that increases of ALT can be part of HBV clearance during therapy with tenofovir,

Use with certain hepatitis C virus antiviral agents
Co-administration of tenofovir disoproxil with ledipasvir / sofosbuvir, sofosbuvir / velpatasvir or sofosbuvir / velpatasvir / voxilaprevir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil and a pharmacokinetic enhancer (ritonavir or cobicistat).

The safety of tenofovir disoproxil in the setting of ledipasvir / sofosbuvir, sofosbuvir / velpatasvir or sofosbuvir / velpatasvir / voxilaprevir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of ledipasvir / sofosbuvir, sofosbuvir / velpatasvir or sofosbuvir / velpatasvir / voxilaprevir with tenofovir disoproxil given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction.

Patients receiving ledipasvir / sofosbuvir, sofosbuvir / velpatasvir or sofosbuvir / velpatasvir / voxilaprevir concomitantly with tenofovir disoproxil and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil.

Weight and metabolic parameters
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate. Mitochondrial dysfunction following exposure in utero. Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune reactivation syndrome
In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis
Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Elderly
Tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir disoproxil.

PREGNANCY AND LACTATION

Pregnancy
A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil. The use of tenofovir disoproxil may be considered during pregnancy, if necessary.

Lactation
Tenofovir has been shown to be excreted in human milk. Therefore, Tenofovir disoproxil fumarate (Hofovir) should not be used during breast-feeding. As a general rule, it is recommended that HIV infected women do not breast-feed their infants in order to avoid transmission of HIV to the infant.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be informed that dizziness has been reported during treatment with tenofovir disoproxil.

DRUG INTERACTIONS

Tenofovir Disoproxil Fumarate should not be administered concomitantly with:
- Medicinal products containing tenofovir disoproxil or tenofovir alafenamide
- Adefovir dipivoxil
- Didanosine
- Renally eliminated medicinal products

Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion via transport proteins hOAT 1, hOAT 3 or MRP 4 (e.g. cidofovir) may increase serum concentrations of tenofovir and/or the co-administered medicinal products.

Use of tenofovir disoproxil should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2.

Given that tacrolimus can affect renal function, close monitoring is recommended when it is co-administered with tenofovir disoproxil.

MAIN SIDE/ ADVERSE EFFECTS

In patients receiving tenofovir disoproxil, rare events of renal impairment, renal failure and uncommon events of proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Tenofovir Disoproxil Fumarate.

Co-administration of Tenofovir disoproxil fumarate (Hofovir) and didanosine is not recommended as this may result in an increased risk of adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Discontinuation of Tenofovir disoproxil fumarate (Hofovir) in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis.

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

Frequency	Tenofovir disoproxil
Metabolism and nutrition disorders:	
Very common	hypophosphataemia[1]
Uncommon	hypokalaemia[1]
Rare	lactic acidosis
Nervous system disorders:	
Very common	dizziness
Gastrointestinal disorders:	
Very common	diarrhoea, vomiting, nausea
Common	flatulence
Uncommon	pancreatitis
Hepatobiliary disorders:	
Common	increased transaminases
Rare	hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders:	
Very common	rash
Rare	angioedema
Musculoskeletal and connective tissue disorders:	
Uncommon	rhabdomyolysis[1], muscular weakness[1]
Rare	osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1, 2], myopathy[1]
Renal and urinary disorders:	
Uncommon	increased creatinine, proximal renal tubulopathy (including Fanconi syndrome)
Rare	acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis)[2], nephrogenic diabetes insipidus
General disorders and administration site conditions:	
Very common	asthenia

[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.
[2] This adverse reaction was identified through post-marketing surveillance.

OVERDOSE

Symptoms
If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Management
Tenofovir can be removed by haemodialysis.

DOSAGE AND ADMINISTRATION

Recommended Dose in Adults
For the treatment of HIV-1 or Chronic hepatitis B: The dose is one 300 mg Tenofovir disoproxil fumarate (Hofovir) tablet once daily taken orally, without regard to food.

Recommended Dose in Renally Impaired Adult Patients:
> CrCl 30-49 mL/min: 300 mg every 48 hours
> CrCl 10-29 mL/min: 300 mg every 72 to 96 hours
> Hemodialysis: 300 mg every 7 days or after approximately 12 hours of dialysis

Recommended Dose in Pediatric Patients (2 to Less Than 18 Years of Age)
HIV-1: In adolescents aged 12 to < 18 years and weighing ≥ 35 kg, the recommended dose of Tenofovir disoproxil fumarate (Hofovir) tablet is 300 mg (one tablet) once daily taken orally with food. The safety and efficacy of tenofovir disoproxil in HIV-1 infected children under 2 years of age have not been established.

Chronic hepatitis B: In adolescents aged 12 to < 18 years and weighing ≥ 35 kg, the recommended dose of Tenofovir disoproxil fumarate (Hofovir) is one tablet once daily, taken orally with food. The optimal duration of treatment is currently unknown. The safety and efficacy of tenofovir disoproxil in children with chronic hepatitis B aged 2 to < 12 years or weighing < 35 kg have not been established.

Caution: Foods, Drugs, Devices & Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

Storage: Store at temperatures not exceeding 30°C. Protect from light.

Presentation/ Packing: White, opaque HDPE bottle with white opaque polypropylene (PP) child resistant cap x 30's (Box of 1 bottle x 30 tablets).

Reg. No.: DRP-12898

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