TEFOD™ Tablets

(Tenofovir Alafenamide)

WARNING: POST-TREATMENT SEVERE ACUTE EXACERBATION OF HEPATITIS B

Discontinuation of anti-hepatitis B therapy, including TEFOD™, may result in severe acute exacerbations of hepatitis B. 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 TEFOD™. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

COMPOSITION

TEFOD™ Tablets 25mg:

Each film coated tablet contains:

Tenofovir Alafenamide (as Fumarate).....25mg

DRUG DESCRIPTION

TEFOD™ is a tablet containing tenofovir alafenamide for oral administration. Tenofovir alafenamide, a hepatitis B virus (HBV) nucleoside analog reverse transcriptase inhibitor, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5•-monophosphate. The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, N- [(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy] methyl] phenoxyphosphinyl]-, 1-methylethylester, (2E)-2-butenedioate (2:1).

It has an empirical formula of $C_{21}H_{29}O_5N_6P•½(C_4H_4O_4)$ and a formula weight of 534.50.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS:

Pharmacotherapeutic group: Antiviral for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors.

ATC code: J05AF13

Mechanism of action: Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is primarily hydrolyzed to form tenofovir by carboxylesterase 1 in primary hepatocytes. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain termination.

Tenofovir has activity that is specific to hepatitis B virus and human immunodeficiency virus (HIV-1 and HIV-2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase • and there is no evidence of mitochondrial toxicity in vitro based on several assays including mitochondrial DNA analyses.

Antiviral activity: The antiviral activity of tenofovir alafenamide was assessed in HepG2 cells against a panel of HBV clinical isolates representing genotypes A-H. The EC50 (50% effective concentration) values for tenofovir alafenamide ranged from 34.7 to 134.4 nM, with an overall mean EC50 of 86.6 nM. The CC50 (50% cytotoxicity concentration) in HepG2 cells was > 44400 nM.

Resistance: ln a pooled analysis of patients receiving tenofovir alafenamide, sequence analysis was performed on paired baseline and on-treatment HBV isolates for patients who either experienced virologic breakthrough (2 consecutive visits with HBV DNA • 69 IU/mL after having been < 69 IU/mL, or 1.0 log10 or greater increase in HBV DNA from nadir) or patients with HBV DNA • 69 IU/mL at Week 96 or at early discontinuation at or after Week 24. ln analyses at Week 48 (N = 20) and Week 96 (N = 72), no amino acid substitutions associated with resistance to tenofovir alafenamide were identified in these isolates (genotypic and phenotypic analyses).

Cross-resistance: The antiviral activity of tenofovir alafenamide was evaluated against a panel of isolates containing nucleos(t)ide reverse transcriptase inhibitor mutations in HepG2 cells. HBV isolates expressing the rtV173L, rtL180M, and rtM204V/I substitutions associated with resistance to lamivudine remained susceptible to tenofovir alafenamide (< 2-fold change in EC50). HBV isolates expressing the rtL180M, rtM204V plus rtT184G, rtS202G, or rtM250V substitutions associated with resistance to entecavir remained susceptible to tenofovir alafenamide. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir remained susceptible to tenofovir alafenamide; however, the HBV isolate expressing rtA181V plus rtN236T exhibited reduced susceptibility to tenofovir alafenamide (3.7-fold change in EC50). The clinical relevance of these substitutions is not known.

PHARMACOKINETICS:

Protein binding: 80% to plasma proteins.

Metabolism: Major elimination pathway, accounting for > 80% of an oral dose. Tenofovir alafenamide (TAF) is converted intracellularly to tenofovir, then phosphorylated to the active tenofovir diphosphate.

Bioavailability: lncreases ~65% with a high-fat meal. This difference in exposure is not considered clinically relevant and it may be administered without regard to food.

Half-life: Tenofovir alafenamide 0.51 hours & tenofovir 32.37 hours.

Time to peak, serum: 0.48 hours

Excretion: Feces (31.7%) and urine (<1%). Unlike tenofovir, tenofovir alafenamide is not a substrate for renal transporters OAT1 and OAT3. The pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

Linearity/Non-linearity: Proportional over the dose range of 8 mg to 125mg.

The pharmacokinetics of tenofovir alafenamide have not been fully evaluated in patients coinfected with HIV and/or hepatitis C virus.

Paediatric population: The pharmacokinetics of tenofovir alafenamide and tenofovir were evaluated in HIV-1-infected, treatment-naïve adolescents who received tenofovir alafenamide (10 mg) given with elvitegravir, cobicistat and emtricitabine as a fixed-dose combination tablet (E/C/F/TAF). No clinically relevant differences in TAF or tenofovir pharmacokinetics were observed between adolescent and adult HIV-1-infected subjects.

INDICATIONS AND DOSAGE

INDICATIONS AND USAGE:

TEFOD™ is indicated for the treatment of chronic hepatitis B in adults and adolescents (aged 12 years and older with body weight at least 35 kg).

Testing: Prior to initiation of TEFOD™, test patients for HIV infection. TEFOD™ alone should not be used in patients with HIV infection. Prior to or when initiating TEFOD™, and during treatment on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. Also assess serum phosphorus in patients with chronic kidney disease.

DOSAGE AND ADMINISTRATION:

Method of Administration: Oral administration. TEFOD™ film-coated tablets should be taken with food.

Dosage: Adults and adolescents (aged 12 years and older with body weight at least 35 kg): one tablet once daily.

Treatment Discontinuation: Treatment discontinuation may be considered as follows:

- HBeAg-positive patients without cirrhosis: Treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or until there is loss of efficacy. Regular reassessment is recommended after treatment discontinuation to detect virological relapse.
- HBeAg-negative patients without cirrhosis: treatment should be administered at least until HBs seroconversion or until there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

Missed Dose: If a dose is missed and less than 18 hours have passed from the time it is usually taken, the patient should take TEFOD™ as soon as possible and then resume their normal dosing schedule. If more than 18 hours have passed from the time it is usually taken, the patient should not take the missed dose and should simply resume the normal dosing schedule.

If the patient vomits within 1 hour of taking TEFOD™, the patient should take another tablet. If the patient vomits more than 1 hour after taking TEFOD™, the patient does not need to take another tablet.

Note: Therapy should be initiated by a physician experienced in the management of chronic hepatitis B.

SPECIAL POPULATIONS:

Paediatric population: The safety and efficacy of tenofovir alafenamide in children younger than 12 years of age, or weighing < 35 kg, have not yet been established. No data are available.

Geriatric population: No dose adjustment of TEFOD® is required in patients aged 65 years and older.

Renal impairment:

CrCl •15 mL/minute: No dosage adjustment necessary.

CrCl <15 mL/minute: Use is not recommended.

ESRD requiring hemodialysis: No dosage adjustment necessary; administer post dialysis on hemodialysis days.

On days of haemodialysis, TEFOD® should be administered after completion of haemodialysis treatment.

No dosing recommendations can be given for patients with CrCl <15mL/min who are not receiving haemodialysis.

Hepatic lmpairment:

Mild impairment (Child-Pugh class A): No dosage adjustment necessary.

Decompensated cirrhosis (Child-Pugh class B or C): Use is not recommended.

OVER DOSAGE:

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with tenofovir alafenamide consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether tenofovir can be removed by peritoneal dialysis.

CONTRAINDICATIONS

TEFOD® is contraindications in patients with previously demonstrated hypersensitivity to any of the components of the product.

WARNINGS AND PRECAUTIONS

CONCERNS RELATED TO ADVERSE EFFECTS:

Lactic acidosis/severe hepatomegaly with steatosis: Lactic acidosis and severe hepatomegaly with steatosis, sometimes fatal, have been reported with the use of nucleoside analogs, alone or in combination with other antiretrovirals. Suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (marked transaminase elevation may/may not accompany hepatomegaly and steatosis).

DISEASE-RELATED CONCERNS:

Severe acute exacerbation of hepatitis B [Boxed Warning]: Discontinuation of anti-hepatitis B therapy may result in severe acute exacerbations of hepatitis B. Monitor clinical and laboratory data closely for several months after treatment discontinuation. If clinically indicated, anti-hepatitis B therapy may be resumed. In patients with advanced liver disease or cirrhosis, discontinuation of anti-hepatitis B therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Patients with decompensated liver disease: There are no data on its safety and efficacy in HBV-infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score > 9 (i.e. class C). 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.

New onset or worsening of renal impairment: Cases of acute renal failure and/or Fanconi syndrome have been reported with use of tenofovir prodrugs; patients with preexisting renal impairment and those taking nephrotoxic agents (including NSAIDs) are at increased risk. Prior to initiation of therapy and during therapy, assess serum creatinine, estimated CrCl, urine protein, and urine glucose in all patients as clinically appropriate; also assess serum phosphorus in patients with chronic kidney disease. Discontinue therapy in patients that develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

There are no safety data on its use to treat HBV-infected patients with CrCl < 30mL/min. The use of TEFOD® is not recommended in patients with CrCl < 15mL/min who are not receiving haemodialysis.

Risk of development of HlV-1 resistance in patients coinfected with HBV and HlV-1: Due to the risk of development of HlV-1 resistance, tenofovir alafenamide is not recommended to give alone for the treatment of HlV-1 infection. The safety and efficacy of tenofovir alafenamide have not been established in patients coinfected with HBV and HlV-1.

HBV transmission: Patients must be advised that TEFOD® does not prevent the risk of transmission of HBV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

Nephrotoxicity: A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded.

Patients co-infected with HBV and hepatitis C or D virus: There are no data on the safety and efficacy of tenofovir alafenamide in patients co-infected with hepatitis C or D virus. Co-administration guidance for the treatment of hepatitis C should be followed.

Hepatitis B and HIV co-infection: HIV antibody testing should be offered to all HBV-infected patients whose HIV-1 infection status is unknown before initiating therapy with TEFOD®. In patients who are co-infected with HBV and HIV, TEFOD® should be co-administered with other antiretroviral agents to ensure that the patient receives an appropriate regimen for treatment of HIV.

CONCURRENT DRUG THERAPY ISSUES:

Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy.

TEFOD® should not be co-administered with products containing tenofovir alafenamide, tenofovir disoproxil fumarate or adefovir dipivoxil. Co-administration of TEFOD® with certain anticonvulsants (e.g. carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g. rifampicin, rifabutin and rifapentine) or St. John's wort, all of which are inducers of P-glycoprotein (P-gp) and may decrease tenofovir alafenamide plasma concentrations, is not recommended.

Co-administration of TEFOD® with strong inhibitors of P-gp (e.g. itraconazole and ketoconazole) may increase tenofovir alafenamide plasma concentrations. Co-administration is not recommended. Consult drug interactions database for more detailed information.

OTHER WARNINGS / PRECAUTIONS:

Monitoring Parameters: Serum creatinine, serum phosphorus (in patients with chronic kidney disease), urine glucose, urine protein (prior to initiation and as clinically indicated during therapy); HIV testing (prior to initiation); hepatic function tests; monitor clinical and laboratory data closely for several months following therapy discontinuation.

SPECIAL POPULATIONS:

Pregnancy: Pregnancy Category B

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of tenofovir alafenamide in pregnant women. However, a large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative nor feto/neonatal toxicity associated with the use of tenofovir disoproxil fumarate. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. The use of TEFOD® may be considered during pregnancy, if necessary.

Lactation: Animal studies have demonstrated that tenofovir is secreted in milk after administration of tenofovir disoproxil fumarate. There is no information regarding the presence of tenofovir alafenamide in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TEFOD® and any potential adverse effects on the breastfed infant from TEFOD® or from the underlying maternal condition. There is insufficient information on the effects of tenofovir in newborns/infants.

Geriatrics population (• 65 years of age): Clinical trials of tenofovir alafenamide did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

TEFOD® has no or negligible influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with TEFOD.

ADVERSE REACTIONS

The following adverse reactions are discussed in other sections but their % occurrence are mentioned below:

Severe Acute Exacerbation of Hepatitis B [Boxed Warning and Warnings and Precautions]
New Onset or Worsening of Renal Impairment [Warnings and Precautions]
Lactic Acidosis/Severe Hepatomegaly with Steatosis [Warnings and Precautions]

>10%:
Central nervous system: Headache (12%)
Neuromuscular & skeletal: Decreased bone mineral density (5% to 11%)

1% TO 10%:
Central nervous system: Fatigue (6%)
Dermatologic: Skin rash and pruritis (<5%)
Endocrine & metabolic: Increased LDL cholesterol (grades 3/4: 6%), glycosuria (grades 3/4: 5%), increased amylase (grades 3/4: 3%)
Gastrointestinal: Abdominal pain (9%), nausea (6%), diarrhea (5%), dyspepsia (5%), flatulence (<5%), vomiting (<5%)
Hepatic: Increased serum alanine aminotransferase (grades 3/4: 8%), increased serum aspartate aminotransferase (grades 3/4: 3%)
Neuromuscular & skeletal: Back pain (6%), arthralgia (5%), increased creatine phosphokinase (grades 3/4: 3%)
Respiratory: Cough (8%)

<1%, POSTMARKETING AND/CASE REPORT:
Skin and Subcutaneous Tissue Disorders: Angioedema, urticaria

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times those observed after human administration. In rats, the study was negative for carcinogenic findings. Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxic assays. No human data on its effect on fertility are available. Animal studies do not indicate harmful effects of tenofovir alafenamide on fertility.

REPORTING OF SUSPECTED ADVERSE REACTIONS:
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals and patients/carers are asked to report any suspected adverse reactions at safety@samikhi.com or call on +92 (0) 21 34383400 (Office hours and out of office hours). Also, adverse event may be reported via website: www.samipharmapk.com

DRUG INTERACTIONS

INTERACTIONS RESULTING IN A CONTRAINDICATION: (NONE)
ESTABLISHED AND OTHER POTENTIALLY SIGNIFICANT INTERACTIONS REQUIRING PRECAUTIONS:

Drug Class: Drug Name[a]	Effect[b]	Clinical Comment
Anticonvulsants: carbamazepine[c,*] oxcarbazepine* phenobarbital* phenytoin*	↓Tenofovir alafenamide	Coadministration of carbamazepine, oxcarbazepine, phenobarbital, or phenytoin, all of which are P-gp inducers, may decrease tenofovir alafenamide plasma concentrations. Based on tenofovir alafenamide population pharmacokinetic and pharmacodynamic analyses. Co-administration is not recommended.
Antifungals: Itraconazole ketoconazole	↑Tenofovir alafenamide	Coadministration of itraconazole or ketoconazole, both of which are P-gp inhibitors, may increase plasma concentrations of tenofovir alafenamide. Co-administration is not recommended.
Antimycobacterial: rifabutin* rifampin* rifapentine*	↓Tenofovir alafenamide	Coadministration of rifampin, rifabutin, and rifapentine, may decrease tenofovir alafenamide plasma concentrations. Coadministration is not recommended.
Herbal Products: St. John's wort* (Hypericum perforatum)	↓Tenofovir alafenamide	Coadministration of St. John's wort, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect. Coadministration is not recommended.
Atazanavir/cobicistat Atazanavir/ritonavir Darunavir/cobicistat Darunavir/ritonavir Lopinavir/ritonavir Tipranavir/ritonavir	↑/effect tenofovir alafenamide	Tipranavir/ritonavir interaction is not studied. It is expected to decrease tenofovir alafenamide. Co-administration is not recommended.

a.This table is not all inclusive. b. ↑= increase, ↓= decrease. c. Indicates that a drug interaction study was conducted. *P-gp inducer.

NO SIGNIFICANT INTERACTION:
Interactions with TEFOD™ Based on drug interaction studies conducted with TEFOD™, no clinically significant drug interactions have been observed with: ethinyl estradiol, itraconazole, ketoconazole, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, dolutegravir, efavirenz, rilpivirine, nevirapine, raltegravir, maraviroc, sofosbuvir, sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir.

POTENTIAL FOR OTHER DRUGS TO AFFECT TENOFOVIR ALAFENAMIDE:
TEFOD™ is a substrate of P-glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption. Drugs that induce P-gp activity are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentrations of tenofovir alafenamide, which may lead to loss of therapeutic effect of TEFOD™. Coadministration of TEFOD™ with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of tenofovir alafenamide.

DRUGS AFFECTING RENAL FUNCTION:
Coadministration of TEFOD™ with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated drugs and this may increase the riskof adverse reactions. Some examples include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs.

STABILITY

See expiry on the pack.

AVAILABILITY

TEFOD™ tablets 25mg in a pack of 30's.

INSTRUCTIONS

Dosage as advised by physician.
To be sold on the prescription of registered medical practitioner.
Keep out of reach of children.
Avoid exposure to heat, light and humidity.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Store in the original package in order to protect from moisture.

Please read the contents carfully before use.
This package insert is regularly reviewed and updated

ٹیفوڈ™ ٹیبلٹ

(ٹینوفوِر ایلافینا مائیڈ)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

دوا کو نمی سے محفوظ رکھنے کے لیے اسکی اصل پیکنگ میں رکھیں۔

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