Tenoread®

Tenofovir Disoproxil Fumarate

FORMS AND PRESENTATION

Tenoread®: 300 mg; Film Coated Tablets; Box of 30.

COMPOSITION

Tenoread®: Each film coated tablet contains tenofovir disoproxil fumarate 300 mg equivalent to 245 mg of tenofovir disoproxil.

Excipients: Lactose monohydrate, croscarmellose sodium, microcrystalline cellulose, starch, magnesium stearate, hypromellose, titanium dioxide, triacetin, FD&C blue.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF07.

Mechanism of action

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 □, □, and □. 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.

Pharmacokinetic properties

Absorption

Following oral administration of tenofovir disoproxil fumarate to HIV infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. Administration of multiple doses of tenofovir disoproxil fumarate with a meal to HIV infected patients resulted in mean (%CV) tenofovir C_{max}, AUC, and C_{min} values of 326 (36.6%) ng/ml, 3,324 (41.2%) ng·h/ml and 64.4 (39.4%) ng/ml, respectively. Maximum tenofovir concentrations are observed in serum within one hour of dosing in the fasted state and within two hours when taken with food. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C_{max} by approximately 14%. Following the first dose of tenofovir disoproxil fumarate in fed patients, the median Cmax in serum ranged from 213 to 375 ng/ml. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir.

Distribution

Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). In vitro protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

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. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

Studies have established the pathway of active tubular secretion of tenofovir to be influx into proximal tubule cell by the human organic anion transporters (hOAT) 1 and 3 and efflux into the urine by the multidrug resistant protein 4 (MRP 4).

INDICATIONS

HIV-1 infection

Tenoread® is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults.

Tenoread® film-coated tablets are also indicated 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.

Hepatitis B infection

Tenoread® is indicated 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.

Tenoread® is indicated 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 listed.

PRECAUTIONS

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 fumarate 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 fumarate 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 fumarate in clinical practice.

Renal monitoring

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with tenofovir disoproxil fumarate 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 fumarate, 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 fumarate 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 fumarate 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 fumarate 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 fumarate and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

NSAIDs: If tenofovir disoproxil fumarate 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 fumarate in combination with a ritonavir or cobicistat boosted protease inhibitor. A close monitoring of renal function is required in these patients.

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): 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.

Adult patients with creatinine clearance < 50 ml/min, including hemodialysis patients:

Tenofovir disoproxil fumarate 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 hemodialysis use of tenofovir disoproxil fumarate is not recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored.

Bone effects

Tenoread® may cause a reduction in BMD.

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 pediatric population

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 pediatric 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 pediatric patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of tenofovir disoproxil fumarate treatment. Interrupting treatment with tenofovir disoproxil fumarate should also be considered in case of progressive decline of renal function when no other cause has been identified.

Renal impairment

The use of tenofovir disoproxil fumarate is not recommended in pediatric patients with renal impairment and should be discontinued in pediatric patients who develop renal impairment during tenofovir disoproxil fumarate therapy.

Bone effects

Tenoread® may cause a reduction in BMD. If bone abnormalities are detected or suspected in pediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.

Liver disease

Safety and efficacy data are very limited in liver transplant patients.

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 due to limited data.

Exacerbations of hepatitis

Flares on treatment: Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterized by transient increases in serum ALT. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis their

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

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 monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines.

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). 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.

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. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation.

Osteonecrosis

Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Elderly

Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir disoproxil fumarate.

Tenoread® contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Effects on ability to drive and use machines

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

FERTILITY, PREGNANCY AND LACTATION

Pregnancy: The use of tenofovir disoproxil fumarate may be considered during pregnancy, if necessary.

Breast-feeding: Tenofovir has been shown to be excreted in human milk. Tenoread® should not be used during breast-feeding.

As a general rule, it is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.

Fertility: There are limited clinical data with respect to the effect of tenofovir disoproxil fumarate on fertility. Animal studies do not indicate harmful effects of tenofovir disoproxil fumarate on fertility.

DRUG INTERACTIONS

Concomitant use not recommended

• Tenoread® should not be administered concomitantly with other medicinal products containing tenofovir disoproxil fumarate or tenofovir alafenamide.

• Tenoread® should not be administered concomitantly with adefovir dipivoxil.

• Didanosine: Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended.

• Renally eliminated medicinal products: Use of tenofovir disoproxil fumarate 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 fumarate.

• Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate (600 mg/200 mg/300 mg q.d.): Co-administration of sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended.

Tenoread® must be taken with food, as food enhances the bioavailability of tenofovir.

ADVERSE EFFECTS

HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil fumarate, 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 Tenoread®.

HIV-1: Approximately one third of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil fumarate in combination with other antiretroviral agents. These reactions are usually mild to moderate gastrointestinal events. Approximately 1% of tenofovir disoproxil fumarate-treated adult patients discontinued treatment due to the gastrointestinal events.

Co-administration of Tenoread® 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.

Hepatitis B: Approximately one quarter of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil fumarate, most of which are mild. In clinical trials of HBV infected patients, the most frequently occurring adverse reaction to tenofovir disoproxil fumarate was nausea (5.4%).

Acute exacerbation of hepatitis has been reported in patients on treatment as well as in patients who have discontinued hepatitis B therapy.

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).

• Metabolism and nutrition disorders: hypophosphataemia (very common); hypokalaemia (uncommon); lactic acidosis (rare).

• Nervous system disorders: dizziness (very common); headache (common).

• Gastrointestinal disorders: diarrhea, vomiting, nausea (very common); abdominal pain, abdominal distension, flatulence (common); pancreatitis (uncommon).

• Hepatobiliary disorders: increased transaminases (common); hepatic steatosis, hepatitis (rare).

• Skin and subcutaneous tissue disorders: rash (very common); angioedema (rare).

• Musculoskeletal and connective tissue disorders: rhabdomyolysis, muscular weakness (uncommon); osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy (rare).

• Renal and urinary disorders: increased creatinine, proximal renal tubulopathy (including Fanconi syndrome) (uncommon); acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus (rare).

• General disorders and administration site conditions: asthenia (very common); fatigue (common).

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.

Posology

The recommended dose of Tenoread® in adults and in adolescents aged 12 to < 18 years and weighing ≥ 35 kg for the treatment of HIV or for the treatment of chronic hepatitis B is 300 mg (one tablet) once daily taken orally with food.

Chronic hepatitis B

The optimal duration of treatment is unknown. Treatment discontinuation may be considered as follows:

- In 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 there is loss of efficacy. Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.
- In HBeAg negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or 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.

Pediatric population

The safety and efficacy of tenofovir disoproxil fumarate in HIV-1 infected children under 2 years of age have not been established. No data are available.

The safety and efficacy of tenofovir disoproxil fumarate in children with chronic hepatitis B aged 2 to < 12 years or weighing < 35 kg have not been established. No data are available.

Missed dose

- If a patient misses a dose of Tenoread® within 12 hours of the time it is usually taken, the patient should take Tenoread® with food as soon as possible and resume normal dosing schedule.
- If a patient misses a dose of Tenoread® by more than 12 hours and it is almost time for their next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.
- If the patient vomits within 1 hour of taking Tenoread®, another tablet should be taken.
- If the patient vomits more than 1 hour after taking Tenoread® they do not need to take another dose.

Special populations

Elderly

No data are available on which to make a dose recommendation for patients over the age of 65 years.

Renal impairment

Moderate renal impairment (creatinine clearance 30-49 ml/min)

For patients unable to take the granule formulation of tenofovir disoproxil fumarate, prolonged dose intervals using the 245 mg film-coated tablets may be used. Administration of 300 mg tenofovir disoproxil as fumarate every 48 hours can be used based on modeling of single-dose pharmacokinetic data in HIV negative and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis, but has not been confirmed in clinical studies. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Severe renal impairment (creatinine clearance < 30 ml/min) and hemodialysis patients

For patients unable to take the granule formulation of tenofovir disoproxil fumarate and with no alternative treatment available, prolonged dose intervals using the 300 mg film-coated tablets may be used as follows:

Severe renal impairment: 300 mg tenofovir disoproxil fumarate may be administered every 72-96 hours (dosing twice a week).

Hemodialysis patients: 300 mg tenofovir disoproxil as fumarate may be administered every 7 days following completion of a hemodialysis session*.

These dose interval adjustments have not been confirmed in clinical studies. Simulations suggest that the prolonged dose interval using Tenoread® 300 mg film-coated tablets is not optimal and could result in increased toxicity and possibly inadequate response. Therefore, clinical response to treatment and renal function should be closely monitored.

* Generally, once weekly dosing assuming three hemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative hemodialysis.

No dosing recommendations can be given for non-hemodialysis patients with creatinine clearance < 10 ml/min.

The use of tenofovir disoproxil fumarate is not recommended in pediatric patients with renal impairment.

Hepatic impairment

No dose adjustment is required in patients with hepatic impairment.

If Tenoread® is discontinued in patients with chronic hepatitis B with or without HIV co-infection, these patients should be closely monitored for evidence of exacerbation of hepatitis.

Method of administration

Tenoread® tablets should be taken once daily, orally with food.

However, in exceptional circumstances Tenoread® 300 mg film-coated tablets can be administered following disintegration of the tablet in at least 100 ml of water, orange juice or grape juice.

OVERDOSAGE

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 hemodialysis; the median hemodialysis clearance of tenofovir is 134 ml/min. It is not known whether tenofovir can be removed by peritoneal dialysis.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Manufactured by Hetero Labs Limited, India
for Benta S.A.L., Lebanon

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

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta S.A.L.,
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