1. NAME OF THE MEDICINAL PRODUCT

ABAVİR® 245mg film-coated tablets

2. QUALITATIVE AND QUANTITIVE COMPOSITION

Active substance:

Tenofovir disoproxil fumarate 300 mg (equivalent to 245 mg Tenofovir disoproxil)

Excipients:

Lactose monohydrate	110 mg
Croscarmellose sodium	53.66 mg
Magnesium stearate	10 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTİCAL FORM

White oval biconvex film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hepatitis B *infection*:

ABAVİR®, in adults

- 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 virüs,
- decompensated liver disease,

indicated for the treatment of chronic hepatitis B.

This indication is based on histologic, virologic, biochemical and serological responses in adult patients with nucleoside and nucleoside experience with HBeAg positive and HBeAg negative chronic hepatitis B with compensated liver function and chronic hepatitis B with decompensated liver function.

ABAVİR® is indicated for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age.

HIV-1 infection:

ABAVİR®, indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults over 18 years

The demonstration of the benefit of ABAVIR® is a study of previously untreated patients, including patients with a high viral load (> 100,000 copies / ml), and an early antiretroviral-treated early virological failure (<10,000 copies / ml, <5,000 copies / ml in most ml) based on the results of studies in which ABAVIR® was added to regular treatment (usually triple treatment) in patients.

ABAVIR® is 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.

The choice of ABAVIR® to treat antiretroviral-experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or treatment history of patients.

4.2 Posology and method of administration

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

Posology / Application frequency and duration:

In exceptional cases, in patients who have difficulty swallowing, ABAVİR® Film Coated Tablet can be used after being dissolved in at least 100 ml of water, orange juice or grape juice.

Method of administration

Adults:

Recommended dose for chronic hepatitis B treatment or HIV treatment is 1 tablet taken with food once a day.

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 (see section 4.4). 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.

Missed dose

If a patient misses a dose of ABAVİR® within 12 hours of the time it is usually taken, the patient should take ABAVİR® with food as soon as possible and resume their normal dosing schedule.

If a patient misses a dose of ABAVİR® 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 ABAVİR® , another tablet should be taken. If the patient vomits more than 1 hour after taking ABAVİR® they do not need to take another dose.

Special populations

Renal impairment:

Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction.

Adults:

There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in adult patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) and long-term safety data has not been evaluated for mild renal impairment (creatinine clearance 50-80 ml/min). Therefore, in adult patients with renal impairment tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks. It is recommended that dose range adjustments be made in adult patients with creatinine clearance < 50 ml/min.

Mild renal impairment (creatinine clearance 50-80 ml/min:

Limited data from clinical studies support once daily dosing of tenofovir disoproxil (as fumarate) in patients with mild renal impairment.

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

Based on modeling single dose pharmacokinetic data in HIV-negative and non-HBV-infected patients with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis, tenofovir disoproxil (as fumarate) is recommended every 48 hours based on modeling; however, this recommendation was not confirmed in clinical trials. Therefore, clinical response to treatment and renal function should be closely monitored in these patients (see sections 4.4 and 5.2).

Severe renal impairment (creatinine clearance < 30 ml/min) and haemodialysis patients
Due to the lack of alternative tablet doses, adequate dosage adjustments can not be applied; Therefore, it is not recommended for use in this patient group. If alternative therapy is not available, prolonged dosing ranges may be used as follows:

Severe renal impairment: 245 mg tenofovir disoproxil (as fumarate) may be administered every 72-96 hours (dosing twice a week).

Hemodialysis patients: Tenofovir disoproxil (as fumarate) can be administered every 7 days after the completion of the hemodialysis session *.

These dose adjustments have not been confirmed in clinical trials. Simulations show that the extended dose range is not optimal and may lead to increased toxicity and possibly insufficient response. Therefore, clinical response to treatment and renal function should be closely monitored (see sections 4.4 and 5.2).

* Generally, assuming three hemodialysis sessions per week, each lasting approximately 4 hours, or once a week after cumulative 12-hour hemodialysis.

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

Hepatic impairment:

No clinically relevant pharmacokinetic changes have been observed in patients with hepatic impairment. For thisreason, no dose adjustment is required in patients with hepatic impairment (see section 5.2)

If ABAVİR®, 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 (see section 4.4).

Paediatric population:

12 years or older infected adolescents with HBV (≥35 kg): One tablet with food once daily. The optimal duration of treatment is not known yet.

12 years or older infected adolescents with HIV (≥35 kg): One tablet with food once daily (see sections 4.4 and 5.l).

Younger than 12 years infected children with HIV or HBV (<35 kg): No data is available for younger children.

Geriatric population:

Elders: No data are available on which to make a dose recommendation for patients over the age of 65 years (see section 4.4).

4.3. Contraindications

ABAVİR®, contraindicated in those who have hypersensitivity to any of the active substance or its excipient.

4.4. Special warnings and precautions for use

General

HIV antibody testing should be offered to all HBV infected patients before initiating tenofovir disoproxil fumarate therapy (see *Co-infection with HIV-1 and 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.

Co-administration of other medicinal products

ABAVİR®, should not be administered concomitantly with other medicinal products containing tenofovir disoproxil fumarate.

Tenofovir disoproksil fumarat should not be administered concomitantly with adefovir dipivoxil.

Co-administration of Tenofovir disoproksil fumarat and didanozinin is not recommended.

Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended. Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see section 4.5).

Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Co-administration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.

Triple treatment with nucleosides / nucleotides

Tenofovir disoproxil fumarate, when combined with lamivudine and abacavir, as well as lamivudine and didanosine in a single dose regimen, has been reported to have a high rate of virological insufficiency and early resistance in HIV patients.

Renal and bone effects in adult population

Renal effects: Tenofovir is mainly excreted from the kidneys. In clinical practice, renal failure, renal failure, high creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate (see Section 4.8).

Renal monitoring

It is recommended that creatinine clearance should be calculated in all patients before initiation of tenofovir disoproxil fumarate treatment, and that renal function (creatinine clearance and serum phosphate) is monitored every four weeks in the first year and then every

three months. Attention should be paid to more frequent monitoring of renal function in patients at risk for renal insufficiency, including patients who previously had kidney problems during adefovir dipivoxil treatment.

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 (see section 4.8, proximal tubulopathy). 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).

Co-administration and risk of renal toxicity:

The use of tenofovir disoproxil fumarate should be avoided in patients who are taking nephrotoxic drugs (eg, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin 2), either recently or simultaneously. If simultaneous use of tenofovir disoproxil fumarate and nephrotoxic agents is unavoidable, renal function should be monitored every week.

Tenofovir disoproxil fumarate has not been clinically evaluated in patients receiving medicinal products secreted by the same route in the kidney by the organic anion transporter (hOAT1) 1 and 3 or 4 MRP (a medical product known to be nephrotoxic, such as cidofovir). This renal carrier (hOAT1) may be responsible for tubular secretion and partly for renal elimination of tenofovir and sidofovir. As a result, the pharmacokinetics of these drugs may change when administered simultaneously. Concurrent use of these drugs is not recommended unless absolutely necessary, but if concurrent use is unavoidable, renal function should be monitored weekly (see section 4.5).

Renal impairment

Renal safety with tenofovir disoproxil fumarate 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 fumarate in patients with impaired renal function.
Therefore, 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 haemodialysis 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 (see sections 4.2 and 5.2).

Bone effects: In a 144-week controlled clinical trial of HIV-infected patients in whom no previous antiretroviral treatment was compared to stavudine and tenofovir disoproxil fumarate in combination with lamivudine and efavirenz, small decreases in bone mineral density of the hip and spine were observed in both treatment groups. Decreases in bone mineral density of the spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group at 144 weeks. Reductions in bone mineral density of the hip were significantly greater in this group until 96 weeks. However, after 144 weeks, the risk of fracture was not increased for clinically relevant bone abnormalities. Bone abnormalities (rarely causing fractures) may be associated with proximal renal tubulopathy (see Section 4.8). If bone abnormalities are suspected or detected, appropriate consultation should be performed.

<u>Renal and bone effects in paediatric population</u>
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 in clinical study GS-US-104-0352 (see sections 4.8 and 5.1).

Renal monitoring

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

Renal management

If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric 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 (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 fumarate treatment.

Co-administration and risk of renal toxicity

The same recommendations apply as in adults (see above).

Renal impairment

The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.2). Tenofovir disoproxil fumarate should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during tenofovir disoproxil fumarate therapy.

Bone effects

ABAVİR® may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown (see section 5.1).

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

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 fumarate 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.

Hepatitis exacerbations during treatment: Spontaneous exacerbations in chronic hepatitis B are characterized by relatively common and transient elevated serum ALT levels. After starting antiviral treatment, serum ALT levels may increase in some patients (see section 4.8). In patients with compensated liver disease, an increase in serum ALT levels is usually not accompanied by an increase in serum bilirubin concentration or liver decompensation. Patients with cirrhosis may be at a higher risk for liver decompensation following an exacerbation of hepatitis and should therefore be closely monitored during treatment.

Flares after treatment discontinuation: Discontinuation of hepatitis B therapy include tenofovir disoproxil fumarate may be associated with severe acute hepatitis exacerbation. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. 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.

Patients who have had tenofovir disoproxil fumarate and have been infected with hepatitis B virus should be monitored closely for at least a few months in terms of both clinical and laboratory follow-up after cessation of treatment. 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 virüs

Co-infection with HIV-1 and hepatitis B: Due to the risk of development of HIV resistance, tenofovir disoproxil fumarate should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients. Patients with pre-existing 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, see above Exacerbations of hepatitis.

Lactic acidosis:

Lactic acidosis, usually associated with hepatosteatosis, has been reported with the use of nucleoside analogues. Preclinical and clinical data suggest that the risk of lactic acidosis, a class effect of nucleoside analogues, is low for tenofovir disoproxil fumarate.

However, this risk can not be ignored because tenofovir is structurally related to nucleoside analogues.

Early symptoms contains (Symptomatic hyperlactatemia), Benign digestive symptoms (nausea, vomiting and abdominal pain), nonspecific malaise, loss of appetite, weight loss, respiratory symptoms (fast and / or deep breathing) or neurological symptoms (motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal insufficiency. Lactic acidosis generally developed a few months after treatment.

Treatment with nucleoside analogues should be discontinued if symptomatic hyperlactatemia and metabolic / lactic acidosis, progressive hepatomegaly or rapidly increasing aminotransferase levels are observed.

Caution should be exercised when administering nucleoside analogues to patients (particularly obese women) with other known risk factors for hepatomegaly, hepatitis or liver disease and hepatosteatosis (some medicinal products including alcoholic). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may also pose a risk.

Patients at high risk should be closely monitored.

Lipodystrophy

CART has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Tenofovir is structurally related to nucleoside analogues hence the risk of lipodystrophy cannot be excluded. However, 144-week clinical data from antiretroviral-naïve HIV infected adult patients indicate that the risk of lipodystrophy was lower with tenofovir disoproxil fumarate than with stavudine when administered with lamivudine and efavirenz.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. 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) 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 fumarate 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 fumarate.

ABAVİR®, 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.

Each dose of medicinal product contains sodium less than 1mmol (23 mg) ; do not expect any side effect related to sodium at this dose.

4.5. Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP450-mediated interactions involving tenofovir with other medicinal products is low.

Concomitant use not recommended

ABAVİR® should not be administered concomitantly with any other medicinal product containing tenofovir disoproxil fumarate.

ABAVİR® should not be administered concomitantly with adefovir dipivoxil.

Didanosine

Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended (see section 4.4 and Table 1).

Renally eliminated medicinal products

Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil fumarate 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 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 (see section 4.4).

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

Other interactions

The interactions between tenofovir disoproxil fumarate and protease inhibitors and antiretroviral agents other than protease inhibitors are listed in Table 1 below (increase "↑", decrease "↓", no change "" ", twice daily" bid "and daily once indicated by "qd").

Table 1: Interactions between tenofovir disoproxil fumarate and other medicinal products

Medicinal product by therapeutic areas (dose in mg)	**Effects on drug levels Mean percent change in AUC, Cmax, Cmin**	**Recommendation concerning coadministration with 245 mg tenofovir disoproxil (as fumarate)**
ANTİ-INFECTIVES		
Antiretrovirals		
Protease inhibitors		

Atazanavir/Ritonavir (300 q.d./100 q.d./300 q.d.)	Atazanavir: AUC: ↓ 25% Cmax: ↓ 28% Cmin: ↓ 26% Tenofovir: AUC: ↑ 37% Cmax: ↑ 34% Cmin: ↑ 29%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Lopinavir/Ritonavir (400 b.i.d./100 b.i.d./300 q.d.)	No significant effect on lopinavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 32% Cmax: ↔ Cmin: ↑ 51%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/Ritonavir/ (300/100 b.i.d./300 q.d.)	Darunavir: No significant effect on darunavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 22% Cmin: ↑ 37%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
NRTIs		
Didanosine	Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60% increase in systemic exposure to	Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended (see section 4.4).

	didanosine that may increase the risk for didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Coadministration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine coadministered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.	
Adefovir dipivoxil	AUC: ↔ Cmax: ↔	Tenofovir disoproxil fumarate should not be administered concurrently with adefovir dipivoxil (see section 4.4).
Entecavir	AUC: ↔ Cmax: ↔	No clinically significant pharmacokinetic interactions

		when tenofovir disoproxil fumarate was coadministered with entecavir.

Studies conducted with other medicinal products

There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate was co-administered with emtricitabine, lamivudine, indinavir, efavirenz, nelfinavir, saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, tacrolimus, or the hormonal contraceptive norgestimate/ethinyl oestradiol.

Tenofovir disoproxil fumarate must be taken with food, as food enhances the bioavailability of tenofovir (see section 5.2).

4.6. Fertility, pregnancy and lactation

General advice:

Pregnancy category : B

If you have potentional pregnancy / contraception

There is no information about Hormonal medicine interaction.

Pregnancy Period

There is no clinical data for use of tenofovir disoproxil fumarate in pregnant woman. Animal studies do not Show harmful effects

Animal studies (see section 5.3) do not show any direct or indirect harmful effects for pregnancy / embryonal / fetal development / birth or development after birth.

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil fumarate. Animal studies do not indicate reproductive toxicity (see section 5.3). 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. There is insufficient information on the effects of tenofovir in newborns/infants. Therefore ABAVİR® should not be used during breast-feeding.

As a general rule, to prevent HIV and HBV transmission to the baby, women infected with HIV and HBV should not breastfeed their babies.

Reproductive ability / Fertility

Limited clinical data are available on the effect of tenofovir disoproxil fumarate on reproductive ability / fertility. Animal studies have not shown the presence of detrimental effects on tenofovir disoproxil fumarate.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with tenofovir disoproxil fumarate.

4.8. Undesirable effects

The below advers effects belong to HIVand HBVpatients who involved clinical sudy and post marketing experiences. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) , rare (≥ 1/10,000 to < 1/1,000), very rare(<1/10.000) or "unknown" (can not be prediction from available evidence). Because, events identified with postmarketing observations, frequency estimates can not be made because they are reported as patients from a population of unknown size.

Summary of the safety profile

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 ABAVİR® (see section 4.4).

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. Tenofovir disoproxil fumarate with lactic acid, steatosis and lipodystrophy were associated with hepatomegaly (seesection 4.4 and 4.8 *Explanation of specific adverse reactions*).

Co-administration of ABAVİR® and didanosine is not recommended as this may result in an increased risk of adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section 4.4).

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 (see section 4.4).

Tabulated summary of adverse reactions
Assessment of adverse reactions for tenofovir disoproxil fumarate is based on safety data from clinical studies and post-marketing experience. All adverse reactions are presented in Table 1.
HIV-1 clinical studies: Assessment of adverse reactions from HIV-1 clinical study data is based on experience in two studies in 653 treatment-experienced patients receiving treatment with tenofovir disoproxil fumarate (n = 443) or placebo (n = 210) in combination with other antiretroviral medicinal products for 24 weeks and also in a double-blind comparative controlled study in which 600 treatment-naïve patients received treatment with tenofovir disoproxil 245 mg (as fumarate) (n = 299) or stavudine (n = 301) in combination with lamivudine and efavirenz for 144 weeks

Hepatitis B clinical studies: Assessment of adverse reactions from HBV clinical study data is primarily based on experience in two double-blind comparative controlled studies in which 641 adult patients with chronic hepatitis B and compensated liver disease received treatment with tenofovir disoproxil 245 mg (as fumarate) daily (n = 426) or adefovir dipivoxil 10 mg daily (n = 215) for 48 weeks. The adverse reactions observed with continued treatment for 288 weeks were consistent with the safety profile of tenofovir disoproxil fumarate.

Patients with decompensated liver disease: The safety profile of tenofovir disoproxil fumarate in patients with decompensated liver disease was assessed in a double-blind active controlled study (GS-US-174-0108) in which adult patients received treatment with tenofovir disoproxil fumarate (n = 45) or emtricitabine plus tenofovir disoproxil fumarate (n = 45) or entecavir (n = 22) for 48 weeks

In the tenofovir disoproxil fumarate treatment arm, 7% of patients discontinued treatment due to an adverse event; 9% of patients experienced a confirmed increase in serum creatinine of ≥ 0.5 mg/dl or confirmed serum phosphate of < 2 mg/dl through week 48; there were no statistically significant differences between the combined tenofovir-containing arms and the entecavir arm. After 168 weeks, 16% (7/45) of the tenofovir disoproxil fumarate group, 4% (2/45) of the emtricitabine plus tenofovir disoproxil fumarate group, and 14% (3/22) of the entecavir group experienced tolerability failure. Thirteen percent (6/45) of the tenofovir disoproxil fumarate group, 13% (6/45) of the emtricitabine plus tenofovir disoproxil fumarate group, and 9% (2/22) of the entecavir group had a confirmed increase in serum creatinine ≥ 0.5 mg/dl or confirmed serum phosphate of < 2 mg/dl.

At week 168, in this population of patients with decompensated liver disease, the rate of death was of 13% (6/45) in the tenofovir disoproxil fumarate group, 11% (5/45) in the emtricitabine plus tenofovir disoproxil fumarate group and 14% (3/22) in the entecavir group. The rate of hepatocellular carcinoma was 18% (8/45) in the tenofovir disoproxil fumarate group, 7% (3/45) in the emtricitabine plus tenofovir disoproxil fumarate group and 9% (2/22) in the entecavir group.

Subjects with a high baseline CPT score were at higher risk of developing serious adverse events (see section 4.4)

Patients with lamivudine-resistant chronic hepatitis B: No new adverse reactions to tenofovir disoproxil fumarate were identified from a randomised, double-blind study (GS-US-174-0121) in which 280 lamivudine-resistant patients received treatment with tenofovir disoproxil fumarate (n = 141) or emtricitabine/tenofovir disoproxil fumarate (n = 139) for 96 weeks.

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) , rare (≥ 1/10,000 to < 1/1,000) or very rare(< 1/10,000), "unknown" (can not be prediction from available evidence).

Table 2: Tabulated summary of adverse reactions associated with tenofovir disoproxil fumarate based on clinical study and post-marketing experience

Frequency	**Tenofovir disoproxil fumarate**
Metabolism and nutrition disorders:	
Very common:	Hypophosphataemia1
Uncommon:	Hypokalaemia1
Rare:	Lactic Acidosis[3]
Nervous system disorders:	
Very common:	Dizziness
Common	Headache
Gastrointestinal disorders:	
Very common:	Diarrhoea, vomiting, nausea
Common:	Abdominal pain, abdominal distension, flatulence
Rare:	Pancreatitis[3]
Hepatobiliary disorders:	
Common:	Increased transaminases
Rare:	Hepatic steatosis[3], Hepatitis
Skin and subcutaneous tissue disorders:	
Very common:	Rash
Rare:	Angioedema
Musculoskeletal and connective tissue disorders:	
Uncommon:	Rhabdomyolysis1, muscular weakness1
Rare:	Osteomalacia (manifested as bone pain and infrequently contributing to fractures)1, 2, myopathy1
Renal and urinary disorders:	
Uncommon:	Increased creatinine
Rare:	Acute renal failure, renal failure, acute tubular necrosis, Proximal renal tubulopathy (including Fanconi syndrome), nefrit (akut interstisyel nefrit dahil)[2], nefrojenik diabetes insipidus

General disorders and administration site conditions:	
Very common:	Asthenia
Common:	Fatigue

[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.

[2] This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical trials or the tenofovir disoproxil fumarate expanded access program. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to tenofovir disoproxil fumarate in randomised controlled clinical trials and the expanded access program (n = 7,319).

[3] For more deails see section 4.8 ***Description of selected adverse reactions***

Description of selected adverse reactions

HIV-1 and hepatitis B:

*Renal impairment:b*As ABAVİR®may cause renal damage monitoring of renal function is recommended (see sections 4.4 and 4.8 *Summary of the safety profile*).

HIV-1:

Interaction with didanosine: Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Lipids, lipodystrophy and metabolic abnormalities:

Antiretroviral combination treatment (CART), has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Antiretroviral combination treatment (CART), has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous

fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see section 4.4).

In a 144-week controlled clinical study in antiretroviral-naïve adult patients that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz, patients who received tenofovir disoproxil had a significantly lower incidence of lipodystrophy compared with patients who received stavudine. The tenofovir disoproxil fumarate arm also had significantly smaller mean increases in fasting triglycerides and total cholesterol than the comparator arm.

Immune reactivation syndrome: In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonekroz: Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Laktik asidoz ve steatozla birlikte şiddetli hepatomegali: Lactic acidosis, usually associated with hepatosteatosis, has been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued if symptomatic hyperlactatemia and metabolic / lactic acidosis, progressive hepatomegaly or rapidly elevated aminotransferase levels are observed (see sec. 4.4).

Hepatit B:
Exacerbations of hepatitis during treatment: In studies with nucleoside-naïve patients, on-treatment ALT elevations > 10 times ULN (upper limit of normal) and > 2 times baseline occurred in 2.6% of tenofovir disoproxil fumarate-treated patients. ALT elevations had a median time to onset of 8 weeks, resolved with continued treatment, and, in a majority of cases, were associated with a ≥ 2 $\log_{10}$ copies/ml reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment (see section 4.4).

Hepatitis exacerbations after discontinuation of therapy: In HBV-infected patients, clinical evidence and laboratory evidence of hepatitis exacerbations after discontinuation of HBV has been observed (see Section 4.4).

Other Special Population

Pediatric population:

Assessment of adverse reactions is based on randomised trials (studies GS-US-104-0321) in 87 HIV-1 infected paediatric patients (aged 12 to < 18 years) who received treatment with tenofovir disoproxil fumarate (n = 45) or placebo/active comparator (n = 42) in combination with other antiretroviral agents for 48 weeks (see section 5.1).

Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents, the BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores observed in subjects who switched to tenofovir disoproxil fumarate were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1).

Of 89 patients (2 to < 12 years) who received tenofovir disoproxil fumarate in study GS-US-104-0352 (median exposure 104 weeks), 4 patients discontinued from the study due to adverse reactions consistent with proximal renal tubulopathy.

Chronic hepatitis B:

Assessment of adverse reactions is based on one randomised study (study GS-US-174-0115) in 106 adolescent patients (12 to < 18 years of age) with chronic hepatitis B receiving treatment with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks. The adverse reactions observed in adolescent patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies of tenofovir disoproxil fumarate in adults (see section 4.8 Tabulated summary of adverse reactions and 5.1).

Reductions in BMD have been observed in HBV infected adolescents. The BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo (see sections 4.4 and 5.1).

Older people: Tenofovir disoproxil fumarate 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 fumarate (see section 4.4).

Patients with renal impairment:
Since tenofovir disoproxil fumarate can cause renal toxicity, close monitoring of renal function is recommended in adult patients with renal impairment treated with ABAVİR® (see sections 4.2, and 4.4). The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see sections 4.2 and 4.4).

Reporting suspected adverse reactions:
It is important to report suspicious drug adverse reactions after licensing. Reporting enables continuous monitoring of the benefit / risk balance of the drug. any adverse reactions in Turkey Pharmacovigilance Center for healthcare professionals (TÜFAM) What must inform (www.titck.gov.t is; e-mail: tufam@titck.gov.t; tel: 00 08 0800314; fax: 0 312 218 35 99).

4.9. Overdose and treatment
If overdose occurs the patient must be monitored for evidence of toxicity (see sections 4.8 and 5.3), and standard supportive treatment applied as necessary.

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

5. PHARMACODYNAMIC PROPERTIES

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

Mechanism of action and pharmacodynamic effects
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.

Data pertaining to HIV

HIV antiviral activity in vitro:

The concentration of tenofovir required for 50% inhibition (EC50) of the wild-type laboratory strain HIV-1IIIB is 1-6 µmol/l in lymphoid cell lines and 1.1 µmol/l against primary HIV-1 subtype B isolates in PBMCs. Tenofovir is also active against HIV-1 subtypes A, C, D, E, F, G, and O and against HIVBaL in primary monocyte/macrophage cells. Tenofovir shows activity in vitro against HIV-2, with an EC50 of 4.9 µmol/l in MT-4 cells.

Resistance: HIV-1 strains with reduced susceptibility to tenofovir and K65R mutation in reverse transcriptase were selected in vitro and in some patients (see Clinical efficacy and safety). Tenofovir disoproxil fumarate should be avoided in patients who have previously received antiretroviral agents with strains harboring the K65R mutation (see section 4.4).

In clinical trials in previously treated patients, anti-HIV activity of 245 mg tenofovir disoproxil (as fumarate) against HIV-1 strains resistant to nucleoside inhibitors was evaluated. The results showed that patients with HIV expressing 3 or more mutations (TAM) related to thymidine analogue (M41L or L210W reverse transcriptase mutation) had reduced responses to the treatment with tenofovir disoproxil (as fuariate).

Clinical efficacy and safety

The effects of tenofovir disoproxil fumarate in treatment-experienced and treatment-naïve HIV-1 infected adults have been demonstrated in trials of 48 weeks and 144 weeks duration, respectively.

In study GS-99-907, 550 treatment-experienced adult patients were treated with placebo or tenofovir disoproxil 245 mg (as fumarate) for 24 weeks. The mean baseline CD4 cell count was 427 cells/mm3, the mean baseline plasma HIV-1 RNA was 3.4 log10 copies/ml (78% of patients had a viral load of < 5,000 copies/ml) and the mean duration of prior HIV treatment was 5.4 years. Baseline genotypic analysis of HIV isolates from 253 patients revealed that 94% of patients had HIV-1 resistance mutations associated with nucleoside reverse transcriptase inhibitors, 58% had mutations associated with protease inhibitors and 48% had mutations associated with non-nucleoside reverse transcriptase inhibitors.

At week 24 the time-weighted average change from baseline in $\log_{10}$ plasma HIV-1 RNA levels ($DAVG_{24}$) was -0.03 $\log_{10}$ copies/ml and -0.61 $\log_{10}$ copies/ml for the placebo and tenofovir disoproxil 245 mg (as fumarate) recipients ($p < 0.0001$). A statistically significant difference in favour of tenofovir disoproxil 245 mg (as fumarate) was seen in the time-weighted average change from baseline at week 24 ($DAVG_{24}$) for CD4 count (+13 cells/mm^3 for tenofovir disoproxil 245 mg (as fumarate) *versus* -11 cells/mm^3 for placebo, p-value = 0.0008). The antiviral response to tenofovir disoproxil fumarate was durable through 48 weeks ($DAVG_{48}$ was -0.57 $\log_{10}$ copies/ml, proportion of patients with HIV-1 RNA below 400 or 50 copies/ml was 41% and 18% respectively). Eight (2%) tenofovir disoproxil 245 mg (as fumarate) treated patients developed the K65R mutation within the first 48 weeks.

The 144-week, double-blind, active controlled phase of study GS-99-903 evaluated the efficacy and safety of tenofovir disoproxil 245 mg (as fumarate) versus stavudine when used in combination with lamivudine and efavirenz in HIV-1 infected adult patients naïve to antiretroviral therapy. The mean baseline CD4 cell count was 279 cells/mm3, the mean baseline plasma HIV-1 RNA was 4.91 log10 copies/ml, 19% of patients had symptomatic HIV-1 infection and 18% had AIDS. Patients were stratified by baseline HIV-1 RNA and CD4 count. Forty-three percent of patients had baseline viral loads > 100,000 copies/ml and 39% had CD4 cell counts < 200 cells/ml.

By intent to treat analysis (missing data and switch in antiretroviral therapy (ART) considered as failure), the proportion of patients with HIV-1 RNA below 400 copies/ml and 50 copies/ml at 48 weeks of treatment was 80% and 76% respectively in the tenofovir disoproxil 245 mg (as fumarate) arm, compared to 84% and 80% in the stavudine arm. At 144 weeks, the proportion of patients with HIV-1 RNA below 400 copies/ml and 50 copies/ml was 71% and 68% respectively in the tenofovir disoproxil 245 mg (as fumarate) arm, compared to 64% and 63% in the stavudine arm.

The average change from baseline for HIV-1 RNA and CD4 count at 48 weeks of treatment was similar in both treatment groups (-3.09 and -3.09 log10 copies/ml; +169 and 167 cells/mm3 in the tenofovir disoproxil 245 mg (as fumarate) and stavudine groups, respectively). At 144 weeks of treatment, the average change from baseline remained similar in both treatment groups (-3.07 and -3.03 log10 copies/ml; +263 and +283 cells/mm3 in the tenofovir disoproxil 245 mg (as fumarate) and stavudine groups, respectively). A consistent response to treatment with tenofovir disoproxil 245 mg (as fumarate) was seen regardless of baseline HIV-1 RNA and CD4 count.

The K65R mutation occurred in a slightly higher percentage of patients in the tenofovir disoproxil fumarate group than the active control group (2.7% versus 0.7%). Efavirenz or lamivudine resistance either preceded or was coincident with the development of K65R in all cases. Eight patients had HIV that expressed K65R in the tenofovir disoproxil 245 mg (as fumarate) arm, 7 of these occurred during the first 48 weeks of treatment and the last one at week 96. No further K65R development was observed up to week 144. One patient in the tenofovir disoproxil (as fumarate) arm developed the K70E substitution in the virus. From both the genotypic and phenotypic analyses there was no evidence for other pathways of resistance to tenofovir.

Data pertaining to HBV

HBV antiviral activity in vitro: The in vitro antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC50 values for tenofovir were in the range of 0.14 to 1.5 µmol/l, with CC50 (50% cytotoxicity concentration) values > 100 µmol/l.

Resistance: No HBV mutations associated with tenofovir disoproxil fumarate resistance have been identified (see Clinical efficacy and safety). In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V mutations associated with resistance to lamivudine and

telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild-type virus. HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V mutations associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6- to 6.9-fold that of wild-type virus. HBV strains expressing the adefovir-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9- to 10-fold that of wild-type virus. Viruses containing the rtA181T mutation remained susceptible to tenofovir with EC50 values 1.5-fold that of wild-type virus.

Clinical efficacy and safety

The demonstration of the benefit of tenofovir disoproxil fumarate is based on responses in adults with compensated liver disease, HBeAg positive and HBeAg negative chronic hepatitis B with clinical evidence that previous treatment has failed.
The treated patients included patients who had never received treatment, had previously received lamivudine, had previously received adefovir dipivoxil and initially had mutations in resistance to lamivudine and / or adefovir dipivoxil. In addition, compensated patients have been shown to benefit from histological responses.

Experience in patients with compensated liver disease at 48 weeks (studies GS-US-174-0102 and GS-US-174-0103):

Results through 48 weeks from two randomised, phase 3 double-blind studies comparing tenofovir disoproxil fumarate to adefovir dipivoxil in adult patients with compensated liver disease are presented in table below. Study GS-US-174-0103 was conducted in 266 (randomised and treated) HBeAg positive patients while study GS-US-174-0102 was conducted in 375 (randomised and treated) patients negative for HBeAg and positive for HBeAb.

In both of these studies tenofovir disoproxil fumarate was significantly superior to adefovir dipivoxil for the primary efficacy endpoint of complete response (defined as HBV DNA levels < 400 copies/ml and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis). Treatment with tenofovir disoproxil 245 mg (as fumarate) was also associated with significantly greater proportions of patients with HBV DNA < 400 copies/ml, when compared to adefovir dipivoxil 10 mg treatment. Both treatments produced similar results with regard to histological response (defined as Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis) at week 48 (see Table 3 below).

In study GS-US-174-0103 a significantly greater proportion of patients in the tenofovir disoproxil fumarate group than in the adefovir dipivoxil group had normalised ALT and achieved HBsAg loss at week 48 (see Table 3 below).

Table 3: Efficacy parameters in compensated HBeAg negative and HBeAg positive patients at week 48

	Study 174-0102 (HBeAg negative)		**Study 174-0103 (HBeAg positive)**	
Parameter	Tenofovir disoproxil 245 mg (as fumarate) n = 250	Adefovir dipivoxil 10 mg n = 125	Tenofovir disoproxil 245 mg (as fumarate) n = 176	Adefovir dipivoxil 10 mg n = 90
Complete response (%)[a]	71*	49	67*	12
Histology				
Histological response (%)[b]	72	69	74	68
Median HBV DNA reduction from baselinec (log10 copies/ml)	- 4.7*	-4.0	-6.4*	-3.7
HBV DNA (%) < 400 copies/ml (< 69 IU/ml)	93*	63	76*	13
ALT (%) Normalised ALTd	76	77	68*	54
Serology (%) HBeAg loss/seroconversion	n/a	n/a	22/21	18/18
HBsAg loss/seroconversion	0/0	0/0	3*/1	0/0

* p-value versus adefovir dipivoxil < 0.05.

[a] Complete response defined as HBV DNA levels < 400 copies/ml and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis,[b] Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis,[c] Median change from baseline HBV DNA merely reflects the difference between baseline HBV DNA and the limit of detection (LOD) of the assay,[d] The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.

n/a = not applicable.

Tenofovir disoproxil fumarate was associated with significantly greater proportions of patients with undetectable HBV DNA (< 169 copies/ml [< 29 IU/ml]; the limit of quantification of the Roche Cobas Taqman HBV assay), when compared to adefovir dipivoxil (study GS-US-174-0102; 91%, 56% and study GS-US-174-0103; 69%, 9%), respectively.

Response to treatment with tenofovir disoproxil fumarate was comparable in nucleoside-experienced (n = 51) and nucleoside-naïve (n = 375) patients and in patients with normal ALT (n = 21) and abnormal ALT (n = 405) at baseline when studies GS-US-174-0102 and GS-US-174-0103 were combined. Forty-nine of the 51 nucleoside-experienced patients were previously treated with lamivudine. Seventy-three percent of nucleoside-experienced and 69% of nucleoside-naïve patients achieved complete response to treatment; 90% of nucleoside-experienced and 88% of nucleoside-naïve patients achieved HBV DNA suppression < 400 copies/ml. All patients with normal ALT at baseline and 88% of patients with abnormal ALT at baseline achieved HBV DNA suppression < 400 copies/ml.

Experience beyond 48 weeks in studies GS-US-174-0102 and GS-US-174-0103
In studies GS-US-174-0102 and GS-US-174-0103, after receiving double-blind treatment for 48 weeks (either tenofovir disoproxil 245 mg (as fumarate) or adefovir dipivoxil 10 mg), patients rolled over with no interruption in treatment to open-label tenofovir disoproxil fumarate. In studies GS-US-174-0102 and GS-US-174-0103, 77% and 61% of patients continued in the study through to 288 weeks, respectively. At weeks 96, 144, 192, and 240 viral suppression, biochemical and serological responses were maintained with continued tenofovir disoproxil fumarate treatment (see Tables 4 and 5 below).

Table 4: Efficacy parameters in compensated HBeAg negative patients at week 96, 144, 192, 240 and 288 open-label treatment

	Study 174-0102 (HBeAg negatif)									
Parameter[a]	Tenofovir disoproxil 245 mg (as fumarate) n=250					Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg (as fumarate) n= 125				
Week	96[b]	144[e]	192[g]	240[i]	288[l]	96[c]	144[f]	192[h]	240[j]	288[m]

HBV DNA (%) <400 copies/ml (<69 IU/ml)	90	87	84	83	80	89	88	87	84	84
ALT (%) Normalised ALT[d]	72	73	67	70	68	68	70	77	76	74
Serology (%) HBeAg loss/ seroconversion	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HBsAg loss/ seroconversion	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0[k]	1/1[n]

[a] Based upon Long Term Evaluation algorithm (LTE Analysis) - Patients who discontinued the study at any time prior to week 384 due to a protocol defined endpoint, as well as those completing week 384, are included in the denominator.

[b] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 48 weeks open-label.

[c] 48 weeks of double-blind adefovir dipivoxil followed by 48 weeks open-label tenofovir disoproxil fumarate.

[d] The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.

[e] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 96 weeks open-label.

[f] 48 weeks of double-blind adefovir dipivoxil followed by 96 weeks open-label tenofovir disoproxil fumarate.

[g] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 144 weeks open-label.

[h] 48 weeks of double-blind adefovir dipivoxil followed by 144 weeks open-label tenofovir disoproxil fumarate.

[i] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 192 weeks open-label.

[j] 48 weeks of double-blind adefovir dipivoxil followed by 192 weeks open-label tenofovir disoproxil fumarate.

[k] One patient in this group became HBsAg negative for the first time at the 240 week visit and was ongoing in the study at the time of the data cut-off. However, the subject's HBsAg loss was ultimately confirmed at the subsequent visit.

[l] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 240 weeks open-label.

[m] 48 weeks of double-blind adefovir dipivoxil followed by 240 weeks open-label tenofovir disoproxil fumarate.

[n] Figures presented are cumulative percentages based upon a Kaplan Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir disoproxil fumarate (KM-TDF).
[o] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 336 weeks open-label.
[p] 48 weeks of double-blind adefovir dipivoxil followed by 336 weeks open-label tenofovir disoproxil fumarate.
n/a = not applicable

Table 5: Efficacy parameters in compensated HBeAg positive patients at week 96, 144, 192, 240 and 288 open-label treatment

	Study 174-0103 (HBeAg pozitive)									
Parameter[a]	Tenofovir disoproxil 245 mg (as fumarate) n = 176					Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg (as fumarate) n = 90				
Week	96[b]	144[e]	192[h]	240[j]	288[m]	96[c]	144[f]	192[i]	240[k]	288[n]
HBV DNA (%) <400 copies/ml (<69 IU/ml)	76	72	68	64	61	74	71	72	66	65
ALT (%) Normalised ALT[d]	60	55	56	46	47	65	61	59	56	57
Serology (%) HBeAg loss/	26/	29/	34/	38/	37/	24/	33/	36/	38/	40/

seroconversion	23	23	25	30	25	20	26	30	31	31
HBsAg loss/ seroconversion	5/4	8/6[g]	11/8[g]	11/8[l]	12/8[l]	6/5	8/7[g]	8/7[g]	10/10[l]	11/10[l]

[a] Based upon Long Term Evaluation algorithm (LTE Analysis) - Patients who discontinued the study at any time prior to week 384 due to a protocol defined endpoint, as well as those completing week 384, are included in the denominator.

[b] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 48 weeks open-label.

[c] 48 weeks of double-blind adefovir dipivoxil followed by 48 weeks open-label tenofovir disoproxil fumarate.

[d] The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.

[e] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 96 weeks open-label.

[f] 48 weeks of double-blind adefovir dipivoxil followed by 96 weeks open-label tenofovir disoproxil fumarate.

[g] Figures presented are cumulative percentages based upon a Kaplan Meier analysis including data collected after the addition of emtricitabine to open-label tenofovir disoproxil fumarate (KM-ITT).

[h] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 144 weeks open-label.

[i] 48 weeks of double-blind adefovir dipivoxil followed by 144 weeks open-label tenofovir disoproxil fumarate.

[j] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 192 weeks open-label.

[k] 48 weeks of double-blind adefovir dipivoxil followed by 192 weeks open-label tenofovir disoproxil fumarate.

[l] Figures presented are cumulative percentages based upon a Kaplan Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir disoproxil fumarate (KM-TDF).

[m] 48 weeks of double-blind tenofovir disoproxil fumarate followed by 240 weeks open-label.

[n] 48 weeks of double-blind adefovir dipivoxil followed by 240 weeks open-label tenofovir disoproxil fumarate.

n/a = not applicable

Paired baseline and week 240 liver biopsy data were available for 331/489 patients who remained in studies GS-US-174-0102 and GS-US-174-0103 at week 240 (see Table 6 below). Ninety-five percent (225/237) of patients without cirrhosis at baseline and 99% (93/94) of patients with cirrhosis at baseline had either no change or an improvement in fibrosis (Ishak fibrosis score). Of the 94 patients with cirrhosis at baseline (Ishak fibrosis score: 5 - 6), 26% (24) experienced no change in Ishak fibrosis score and 72% (68) experienced regression of cirrhosis by week 240 with a reduction in Ishak fibrosis score of at least 2 points.

Table 6: Histological response (%) in compensated HBeAg negative and HBeAg positive subjects at week 240 compared to baseline

	Study 174-0102 (HBeAg negative)		**Study 174-0103 (HBeAg positive)**	
	Tenofovir disoproxil 245 mg (as fumarate) n = 250[c]	Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg (as fumarate) n = 125[d]	Tenofovir disoproxil 245 mg (as fumarate) n = 176[c]	Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg (as fumarate) n = 90[d]
Histological response[a,b] (%)	88 [130/148]	85 [63/74]	90 [63/70]	92 [36/39]

[a] The population used for analysis of histology included only patients with available liver biopsy data (Missing = Excluded) by week 240. Response after addition of emtricitabine is excluded (total of 17 subjects across both studies).

[b] Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.

[c] 48 weeks double-blind tenofovir disoproxil fumarate followed by up to 192 weeks open-label.

[d] 48 weeks double-blind adefovir dipivoxil followed by up to 192 weeks open-label tenofovir disoproxil fumarate.

Experience in patients with HIV co-infection and prior lamivudine experience:

In a randomised, 48-week double-blind, controlled study of tenofovir disoproxil 245 mg (as fumarate) in adult patients co-infected with HIV-1 and chronic hepatitis B with prior lamivudine experience (study ACTG 5127), the mean serum HBV DNA levels at baseline in patients randomised to the tenofovir arm were 9.45 log10 copies/ml (n = 27). Treatment with tenofovir disoproxil 245 mg (as fumarate) was associated with a mean change in serum HBV DNA from baseline, in the patients for whom there was 48-week data, of -5.74 log10 copies/ml (n = 18). In addition, 61% of patients had normal ALT at week 48.

Experience in patients with persistent viral replication

The efficacy and safety of tenofovir disoproxil 245 mg (as fumarate) or tenofovir disoproxil 245 mg (as fumarate) plus 200 mg emtricitabine has been evaluated in a randomised, double-blind study (study GS-US-174-0106), in HBeAg positive and HBeAg negative adult patients who had persistent viraemia (HBV DNA ≥ 1,000 copies/ml) while receiving adefovir dipivoxil 10 mg for more than 24 weeks. At baseline, 57% of patients randomised to tenofovir disoproxil fumarate versus 60% of patients randomised to emtricitabine plus tenofovir disoproxil fumarate treatment group had previously been treated with lamivudine. Overall at week 24, treatment with tenofovir disoproxil fumarate resulted in 66% (35/53) of patients with HBV DNA < 400 copies/ml (< 69 IU/ml) versus 69% (36/52) of patients treated with emtricitabine plus tenofovir disoproxil fumarate (p = 0.672). In addition 55% (29/53) of patients treated with tenofovir disoproxil fumarate had undetectable HBV DNA (< 169 copies/ml [< 29 IU/ml]; the limit of quantification of the Roche Cobas TaqMan HBV assay) versus 60% (31/52) of patients treated with emtricitabine plus tenofovir disoproxil fumarate (p = 0.504). Comparisons between treatment groups beyond week 24 are difficult to interpret since investigators had the option to intensify treatment to open-label emtricitabine plus tenofovir disoproxil. Long-term studies to evaluate the benefit/risk of bitherapy with emtricitabine plus tenofovir disoproxil fumarate in HBV monoinfected patients are ongoing.

Experience in patients with decompensated liver disease at 48 weeks (study GS-US-174-0108); Study GS-US-174-0108 is a randomised, double-blind, active controlled study evaluating the safety and efficacy of tenofovir disoproxil fumarate (n = 45), emtricitabine plus tenofovir disoproxil fumarate (n = 45), and entecavir (n = 22), in patients with decompensated liver disease. In the tenofovir disoproxil fumarate treatment arm, patients had a mean CPT score of 7.2, mean HBV DNA of 5.8 log10 copies/ml and mean serum ALT of 61 U/l at baseline. Forty-two percent (19/45) of patients had at least 6 months of prior lamivudine experience, 20% (9/45) of patients had prior adefovir dipivoxil experience and 9 of 45 patients (20%) had lamivudine and/or adefovir dipivoxil resistance mutations at baseline. The co-primary safety endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine ≥ 0.5 mg/dl or confirmed serum phosphate of < 2 mg/dl.

In patients with CPT scores ≤ 9, 74% (29/39) of tenofovir disoproxil fumarate, and 94% (33/35) of emtricitabine plus tenofovir disoproxil fumarate treatment groups achieved HBV DNA < 400 copies/ml after 48 weeks of treatment.

Overall, the data derived from this study are too limited to draw any definitive conclusions on the comparison of emtricitabine plus tenofovir disoproxil fumarate versus tenofovir disoproxil fumarate, (see Table 7 below).

Table 7: Safety and efficacy parameters in decompensated patients at week 48

	Study 174-0108		
Parameter	Tenofovir disoproxil 245 mg (as fumarate) (n = 45)	Emtricitabine 200 mg/ tenofovir disoproxil 245 mg (as fumarate) (n = 45)	Entecavir (0.5 mg or 1 mg) n = 22
Tolerability failure (permanent discontinuation of study drug due to a treatment emergent AE)	3 (%7)	2 (%4)	2 (%9)

n (%)[a]			
Confirmed increase in serum creatinine ≥ 0.5 mg/dl from baseline or confirmed serum phosphate of < 2 mg/dl n (%)[b]	4 (%9)	3 (%7)	1(%5)
HBV DNA n (%) < 400 copies/ml n (%)	31/44 (%70)	36/41(%88)	16/22 (%73)
ALT n (%) Normal ALT	25/44 (%57)	31/41 (%76)	12/22 (%55)
≥ 2 point decrease in CPT from baseline n (%) n (%)	7/27 (%26)	12/25 (%48)	5/12 (%42)
Mean change from baseline in CPT score	-0.8	-0.9	-1.3
Mean change from baseline in MELD score	-1.8	-2.3	-2.6

[a] p-value comparing the combined tenofovir-containing arms versus the entecavir arm = 0.622,

[b] p-value comparing the combined tenofovir-containing arms versus the entecavir arm = 1.000.

Experience beyond 48 weeks in study GS-US-174-0108

Using a noncompleter/switch = failure analysis, 50% (21/42) of subjects receiving tenofovir disoproxil fumarate, 76% (28/37) of subjects receiving emtricitabine plus tenofovir disoproxil fumarate and 52% (11/21) of subjects receiving entecavir achieved HBV DNA < 400 copies/ml at week 168..

Experience in patients with lamivudine-resistant HBV at 96 weeks (study GS-US-174-0121)

The efficacy and safety of 245 mg tenofovir disoproxil (as fumarate) was evaluated in a randomised, double-blind study (GS-US-174-0121) in HBeAg positive and HBeAg negative patients (n = 280) with compensated liver disease, viraemia (HBV DNA ≥ 1,000 IU/ml), and genotypic evidence of lamivudine resistance (rtM204I/V +/- rtL180M). Only five had adefovir-associated resistance mutations at baseline. One hundred forty-one and 139 adult subjects were randomised to a tenofovir disoproxil fumarate and emtricitabine plus tenofovir disoproxil fumarate treatment arm, respectively. Baseline demographics were similar between the two treatment arms: At baseline, 52.5% of subjects were HBeAg negative, 47.5% were HBeAg positive, mean HBV DNA level was 6.5 log10 copies/ml, and mean ALT was 79 U/l, respectively.

After 96 weeks of treatment, HBV DNA <400 copies / ml was observed in 126 (89%) of 141 volunteers randomized to tenofovir disoproxil fumarate, and ALT normalization was found in 49 (62%) of 79 volunteers. After 96 weeks of treatment with emtricitabine plus tenofovir disoproxil fumarate, HBV DNA <400 copies / ml in 139 (86%) and ALT normalization was observed in 52 (63%) of 139 volunteers. In HBeAg positive volunteers randomized to tenofovir disoproxil fumarate, HBeAg loss was observed in 10 (65%) out of 65 volunteers by the 96th week and anti-HBe seroconversion was observed in 7 (11%) of 65 volunteers. In HBeAg positive volunteers randomized to emtricitabine plus tenofovir disoproxil fumarate, HBeAg loss was seen in 9 out of 68 (13%) by 96 weeks and anti-HBe seroconversion was seen in 7 out of 68 (10%). None of the patients randomized to tenofovir disoproxil fumarate had HBsAg loss or seroconversion to anti-HBs. HBeAg loss was observed in a volunteer randomized to emtricitabine arthritis tenofovir disoproxil fumarate.

Clinical resistance

Four hundred and twenty-six HBeAg negative (GS-US-174-0102, n = 250) and HBeAg positive (GS-US-174-0103, n = 176) patients initially randomised to double-blind tenofovir disoproxil fumarate treatment and then switched to open-label tenofovir disoproxil fumarate treatment were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations performed on all patients with HBV DNA > 400 copies/ml at week 48 *(n = 39), 96 (n = 24), 144 (n = 6), 192 (n = 5), 240 (n = 4), 288 (n = 6) and 384 (n = 2)* of tenofovir disoproxil fumarate monotherapy showed that no mutations associated with tenofovir disoproxil fumarate resistance have developed.

Two hundred and fifteen HBeAg negative (GS-US-174-0102, n = 125) and HBeAg positive (GS-US-174-0103, n = 90) patients initially randomised to double-blind adefovir dipivoxil treatment and then switched to open-label tenofovir disoproxil fumarate treatment were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations performed on all patients with HBV DNA > 400 copies/ml at week 48 (n = 16), 96 (n = 5), 144 (n = 1), 192 (n = 2), 240 (n = 1), 288 (n = 1) and 384 (n = 2) of tenofovir disoproxil fumarate monotherapy showed that no mutations associated with tenofovir disoproxil fumarate resistance have developed.
In study GS-US-174-0108, 45 patients (including 9 patients with lamivudine and/or adefovir dipivoxil resistance mutations at baseline) received tenofovir disoproxil fumarate for up to 168 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/8 patients with HBV DNA > 400 copies/ml at week 48. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates. Genotypic analysis was conducted for 5 subjects in the tenofovir disoproxil fumarate arm post week 48. No amino acid substitutions associated with tenofovir disoproxil fumarate resistance were detected in any subject.

In study GS-US-174-0121, 141 patients with lamivudine resistance substitutions at baseline received tenofovir disoproxil fumarate for up to 96 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6 of 9 patients with HBV DNA > 400 copies/ml at their last time point on tenofovir disoproxil fumarate. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.

In a paediatric study (GS-US-174-0115), 52 patients (including 6 patients with lamivudine resistance mutations at baseline) received tenofovir disoproxil fumarate for up to 72 weeks. Genotypic evaluations were performed on all patients with HBV DNA > 400 copies/ml at week 48 (n = 6) and week 72 (n = 5). No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.

Paediatric population
HIV-1: In study GS-US-104-0321, 87 HIV-1 infected treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. Due to limitations of the study, a benefit of tenofovir disoproxil fumarate over placebo was not demonstrated

based on plasma HIV-1 RNA levels at week 24. However, a benefit is expected for the adolescent population based on extrapolation of adult data and comparative pharmacokinetic data (see section 5.2).

In patients who received treatment with tenofovir disoproxil fumarate or placebo, mean lumbar spine BMD Z-score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double-blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil fumarate and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil fumarate group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil fumarate group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil fumarate, BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body.

In study GS-US-104-0352, 97 treatment-experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (n = 48) or continue on their original regimen (n = 49) for 48 weeks. At week 48, 83% of patients in the tenofovir disoproxil fumarate treatment group and 92% of patients in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations < 400 copies/ml. The difference in the proportion of patients who maintained < 400 copies/ml at week 48 was mainly influenced by the higher number of discontinuations in the tenofovir disoproxil fumarate treatment group. When missing data were excluded, 91% of patients in the tenofovir disoproxil fumarate treatment group and 94% of patients in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations < 400 copies/ml at week 48.

Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil fumarate, or stavudine or zidovudine, **mean lumbar spine BMD Z-score** *was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at* **week 48 (***end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil fumarate and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil fumarate treatment group and the stavudine or zidovudine treatment group. Total*

body bone gain was less in the tenofovir disoproxil fumarate treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil fumarate treated subject and no stavudine or zidovudine treated subjects experienced **significant (> 4%) lumbar spine BMD loss** *at* **week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. BMD Z-scores were not adjusted for height and weight.**

In study GS-US-104-0352, 4 out of 89 paediatric patients exposed to *tenofovir disoproxil fumarate* **discontinued due to adverse reactions consistent with proximal renal tubulopathy (median** *tenofovir disoproxil fumarate* **exposure 104 weeks).**

Chronic hepatitis B: In study GS-US-174-0115, 106 HBeAg negative and HBeAg positive patients aged 12 to < 18 years with chronic HBV infection [HBV DNA ≥ 105 copies/ml, elevated serum ALT (≥ 2 x ULN) or a history of elevated serum ALT levels in the past 24 months] were treated with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks. Subjects must have been naïve to tenofovir disoproxil fumarate, but could have received interferon based regimens (> 6 months prior to screening) or any other non-tenofovir disoproxil fumarate containing oral anti-HBV nucleoside/nucleotide therapy (> 16 weeks prior to screening). At week 72, overall 88% (46/52) of patients in the tenofovir disoproxil fumarate treatment group and 0% (0/54) of patients in the placebo group had HBV DNA < 400 copies/ml. Seventy-four percent (26/35) of patients in the tenofovir disoproxil fumarate group had normalised ALT at week 72 compared to 31% (13/42) in the placebo group. Response to treatment with tenofovir disoproxil fumarate was comparable in nucleos(t)ide-naïve (n = 20) and nucleos(t)ide-experienced (n = 32) patients, including lamivudine-resistant patients (n = 6). Ninety-five percent of nucleos(t)ide-naïve patients, 84% of nucleos(t)ide-experienced patients, and 83% of lamivudine-resistant patients achieved HBV DNA < 400 copies/ml at week 72. Thirty-one of the 32 nucleos(t)ide-experienced patients had prior lamivudine experience. *At week 72, 96% (27/28) of immune-active patients (HBV DNA ≥ 105 copies/ml, serum ALT > 1.5 x ULN) in the tenofovir disoproxil fumarate treatment group and 0% (0/32) of patients in the placebo group had HBV DNA < 400 copies/ml. Seventy-five percent (21/28) of immune-active patients in the tenofovir disoproxil fumarate group had normal ALT at week 72 compared to 34% (11/32) in the placebo group.*

No subjects met the primary safety endpoint of a 6% decrease in lumbar spine BMD. In subjects receiving tenofovir disoproxil fumarate or placebo, mean (SD) lumbar spine BMD Z-score was -0.43 (0.764) and -0.28 (0.813), and mean total body BMD Z-score was -0.20 (1.126) and -0.26 (0.878), respectively, at baseline. The mean (SD) change in lumbar spine BMD Z-score from baseline to week 72 in subjects receiving tenofovir disoproxil fumarate was -0.05 (0.310) and 0.07 (0.377) in those receiving placebo. The mean change in whole body BMD Z-score in subjects receiving tenofovir disoproxil fumarate was -0.15 (0.379) and 0.06 (0.361) in those receiving placebo**. BMD Z-scores were not adjusted for height and weight.** The mean percentage increase in whole body and lumbar spine BMD from baseline to week 72 was 2.84% and 4.95%, respectively, in subjects receiving tenofovir disoproxil fumarate. These mean percentage increases in whole body and lumbar spine BMD were 2.53% and 3.19% less, respectively, when compared to subjects receiving placebo. Three subjects in the tenofovir disoproxil fumarate group and 2 subjects in the placebo group had a decrease of > 4% in spine BMD.

5.2. Pharmacokinetic Properties

General Properties:

Tenofovir disoproxil fumarate 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 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 Cmax, AUC, and Cmin 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 Cmax 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.

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.

Biotransformation

In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (approximately 300-fold) than those observed *in vivo*, tenofovir did not inhibit in vitro drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation (CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2).

Tenofovir disoproxil fumarate at a concentration of 100 µmol/l had no effect on any of the CYP450 isoforms, except CYP1A1/2, where a small (6%) but statistically significant reduction in metabolism of CYP1A1/2 substrate was observed. İt had no effect on any other CYP450 isoform. Based on these data, it is unlikely that clinically significant interactions involving tenofovir disoproxil fumarate and medicinal products metabolised by CYP450 would occur.

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).

Linearity/non-linearity

The pharmacokinetics of tenofovir were independent of tenofovir disoproxil fumarate dose over the dose range 75 to 600 mg and were not affected by repeated dosing at any dose level.

Characteristic of patients:

Elders:

Pharmacokinetic studies have not been performed in the elderly (over 65 years of age).

Gender

Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect.

Ethnicity:

Pharmacokinetics have not been specifically studied in different ethnic groups.

Paediatric population

HIV-1: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected adolescent patients (aged 12 to < 18 years) with body weight ≥ 35 kg. Mean (± SD) Cmax and AUCtau are 0.38 ± 0.13 μg/ml and 3.39 ± 1.22 μg•h/ml, respectively. Tenofovir exposure achieved in adolescent patients receiving oral daily doses of tenofovir disoproxil 245 mg (as fumarate) was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg (as fumarate).

Chronic hepatitis B: Steady-state tenofovir exposure in HBV infected adolescent patients (12 to < 18 years of age) receiving an oral daily dose of tenofovir disoproxil 245 mg (as fumarate) was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg (as fumarate).

Pharmacokinetic studies have not been performed with tenofovir disoproxil (as fumarate) 245 mg tablets in children under 12 years or with renal impairment.

Renal impairment

Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil 245 mg to 40 non-HIV, non-HBV infected adult patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2,185 (12%) ng•h/ml in subjects with CrCl > 80 ml/min to respectively 3,064 (30%) ng•h/ml, 6,009 (42%) ng•h/ml and 15,985 (45%) ng•h/ml in patients with mild, moderate and severe renal impairment. The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower Cmin levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean Cmax of 1,032 ng/ml and a mean AUC0-48h of 42,857 ng•h/ml.
It is recommended that the dosing interval for tenofovir disoproxil 245 mg (as fumarate) is modified in adult patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis (see section 4.2).

The pharmacokinetics of tenofovir in non-haemodialysis patients with creatinine clearance < 10 ml/min and in patients with ESRD managed by peritoneal or other forms of dialysis have not been studied.

The pharmacokinetics of tenofovir in paediatric patients with renal impairment have not been studied. No data are available to make dose recommendations (see sections 4.2 and 4.4).

Hepatic impairment

A single 245 mg dose of tenofovir disoproxil was administered to non-HIV, non-HBV infected adult patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir Cmax and AUC0-∞ values were 223 (34.8%) ng/ml and 2,050 (50.8%) ng•h/ml, respectively, in normal subjects compared with 289

(46.0%) ng/ml and 2,310 (43.5%) ng•h/ml in subjects with moderate hepatic impairment, and 305 (24.8%) ng/ml and 2,740 (44.0%) ng•h/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics

In non-proliferating human peripheral blood mononuclear cells (PBMCs) the half-life of tenofovir diphosphate was found to be approximately 50 hours, whereas the half-life in phytohaemagglutinin-stimulated PBMCs was found to be approximately 10 hours.

5.3. Precilinical Safety Data

Non-clinical safety pharmacology studies reveal no special hazard for humans.

Findings in repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

Genotoxicity studies revealed positive results in the in vitro mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an UDS test in primary rat hepatocytes. However, it was negative in an in vivo mouse bone marrow micronucleus assay

Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumours at an extremely high dose in mice. These tumours are unlikely to be of relevance to humans.

Reproductive studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet Core

Croscarmellose sodium
Lactose monohydrate
Microcrystalline Cellulose
Starch pregelatinised
Magnesium stearate

Film Coating
Opadry II White 32K18425 (Titanium dioxide, lactose monohydrate, Triacetin hypromellose)

6.2 Incompabilities
Nor applicable

6.3 Shelf Life
24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Store at room temperature below 25oC and protect from light. Store in the original package. Close bottle cap tightly.

6.5 Nature and contents of container
ABAVİR® 245mg Film Coated Tablet is contained in an HDPE bottle with a child-proof cap and a silica gel desiccant. Package size is 30 and 90 tablets.

6.6 Special precautions for disposal and other handling
Unused products or waste materials must be disposed of in accordance with the Kontrolü Regulation on the Control of Medical Products ”and the Kontrolü Regulation on the Control of Packaging Wastes”.

7 MARKETING AUTHORISATION HOLDER
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