AUSTRALIAN PRODUCT INFORMATION

TENOFOVIR DISOPROXIL VIATRIS

Tenofovir disoproxil maleate film coated tablets

1 NAME OF THE MEDICINE

Tenofovir disoproxil maleate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TENOFOVIR DISOPROXIL VIATRIS tablet contains 300 mg of tenofovir disoproxil as maleate (equivalent to 245 mg of tenofovir disoproxil) as the active ingredient.

Excipients with known effect: Sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

TENOFOVIR DISOPROXIL VIATRIS (tenofovir disoproxil maleate) 300 mg: Light blue colored, 12 mm round, biconvex, film coated tablets debossed with 'TM300' on one side of the tablet and 'M' on other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TENOFOVIR DISOPROXIL VIATRIS in combination with other antiretroviral agents is indicated for the treatment of HIV infected adults and paediatric patients 12 years of age and older.

TENOFOVIR DISOPROXIL VIATRIS is indicated for the treatment of chronic hepatitis B in adults (see Section 5.1 PHARMACODYNAMIC PROPERTIES: Clinical trials).

TENOFOVIR DISOPROXIL VIATRIS is indicated for the treatment of chronic hepatitis B in paediatric patients 12 years of age and older with compensated liver disease and with evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels or evidence of active inflammation.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults:

The recommended dose is 300 mg (one tablet) once daily taken orally. In order to optimise the absorption of tenofovir, it is recommended that TENOFOVIR DISOPROXIL VIATRIS be taken with food.

Paediatric Patients (≥ 12 Years of Age and ≥ 35 kg):

The recommended dose for paediatric patients (12 years of age and older), who weigh ≥ 35 kg, is 300 mg (one tablet) once daily taken orally. In order to optimise the absorption of tenofovir, it is recommended that TENOFOVIR DISOPROXIL VIATRIS be taken with food.

The safety and efficacy of tenofovir disoproxil in patients under the age of 12 years have not been established. TENOFOVIR DISOPROXIL VIATRIS must not be administered to children under 12, until further data become available.

Elderly:

No data are available on which to make a dose recommendation for patients over the age of 65 years. The safety and efficacy of tenofovir disoproxil have not been established in patients over the age of 65 years. Caution should be exercised when administering TENOFOVIR DISOPROXIL VIATRIS to elderly patients until further data become available describing the disposition of tenofovir disoproxil in these patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The greater frequency of decreased

hepatic, renal or cardiac function in these patients, presence of any concomitant illnesses or the need for treatment with other medicinal products concomitantly with TENOFOVIR DISOPROXIL VIATRIS should be taken into consideration.

Renal impairment:

Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. Dosing interval adjustment is required in all patients with creatinine clearance <50 ml/min (calculated using the Cockcroft Gault equation), as detailed in Table 1 below. The proposed dose interval modifications are based on limited data and may not be optimal. The safety and efficacy of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Table 1. Dosage Adjustment for Patients with Altered Creatinine Clearance

Creatinine Clearance (mL/min)[1]				Haemodialysis Patients
	≥50	30–49	10–29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[2]

1. Calculated with Cockcroft Gault equation.
2. Generally once weekly assuming three haemodialysis sessions a week of approximately 4 hours duration. TENOFOVIR DISOPROXIL VIATRIS should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-haemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients.

No data are available to make dose recommendations in paediatric patients 12 years of age and older with renal impairment.

Hepatic impairment:

There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in TENOFOVIR DISOPROXIL VIATRIS dosing is required in patients with hepatic impairment.

Chronic hepatitis B:

Treatment with TENOFOVIR DISOPROXIL VIATRIS may be discontinued if there is HBsAg loss or HBsAg seroconversion, otherwise the optimal duration of treatment is unknown.

4.3 CONTRAINDICATIONS

Known hypersensitivity to tenofovir, tenofovir disoproxil maleate, tenofovir disoproxil fumarate or to any of the excipients in the film-coated tablets.

TENOFOVIR DISOPROXIL VIATRIS must not be administered to children less than 12 years of age until further data become available.

TENOFOVIR DISOPROXIL VIATRIS should not be administered concurrently with fixed dose combination tablets containing tenofovir disoproxil maleate, tenofovir disoproxil fumarate, tenofovir alafenamide or adefovir dipivoxil.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General:

Patients receiving tenofovir disoproxil therapy or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Patients should be advised that antiretroviral therapies, including TENOFOVIR DISOPROXIL VIATRIS, have not been proven to prevent the risk of transmission of HIV or HBV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that tenofovir is not a cure for HIV infection.

HIV antibody testing should be offered to all HBV-infected patients before initiating tenofovir therapy (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: HIV and HBV co-infection).

In the treatment of chronic hepatitis B, limited data are currently available in immuno-suppressed patients or those receiving immuno-suppressive regimens, orthotrophic liver transplant patients and patients coinfected with the hepatitis C or D virus. As clinical studies have not included sufficient numbers of subjects to determine whether these patients respond differently to tenofovir chronic hepatitis B therapy, such patients should be closely monitored

Use in Renal Impairment

Dosing interval adjustment is required in all patients with creatinine clearance <50 ml/min (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION). The proposed dose interval modifications are based on limited data and may not be optimal. The safety and efficacy of these dosing interval adjustment guidelines have not been clinically evaluated, and so the potential benefit of tenofovir therapy should be assessed against the potential risk of renal toxicity. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia), has been reported in association with the use of tenofovir disoproxil (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Post Marketing Experience).

TENOFOVIR DISOPROXIL VIATRIS should be avoided with concurrent or recent use of a nephrotoxic agent.

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy and, as clinically appropriate, during tenofovir therapy. Patients at risk for, or with a history of, renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, should be routinely monitored for changes in serum creatinine and phosphorus.

Use in the Elderly

Tenofovir disoproxil has not been studied in patients over the age of 65. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric Use

The safety and efficacy of tenofovir in paediatric patients aged 12 to <18 years is supported by data from two randomised studies in which tenofovir disoproxil was administered to HIV-infected treatment experienced patients and patients with chronic hepatitis B (see Section 5.1 PHARMACODYNAMIC PROPERTIES: Clinical trials and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). The safety and efficacy of tenofovir disoproxil have not been established in children less than 12 years of age.

The clinical relevance of the long term effects of tenofovir disoproxil treatment on BMD are unknown, and at present the data on the reversibility of renal toxicity effects is limited. Therefore, a multidisciplinary approach is recommended to consider the benefit/risk balance of treatment.

As hepatitis B is a chronic disease of the liver, ongoing clinical monitoring is recommended.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including tenofovir disoproxil, in the treatment of HIV infection. A majority of these cases have been reported in women. The preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, a class effect of nucleoside analogues is low for tenofovir disoproxil. However, as tenofovir is structurally related to nucleoside analogues, this risk cannot be excluded. Caution should be exercised when administering TENOFOVIR DISOPROXIL VIATRIS to any patient, and particularly to those with known risk factors for liver disease. Treatment with TENOFOVIR DISOPROXIL VIATRIS should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

HIV and HBV co-infection

Due to the risk of development of HIV resistance, TENOFOVIR DISOPROXIL VIATRIS should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients.

Exacerbation of Hepatitis After Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including tenofovir may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue tenofovir treatment should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, discontinuation of anti-hepatitis B therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Early Virologic Failure

Clinical studies in HIV-infected patients have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance mutations have been reported in clinical studies of combinations of tenofovir disoproxil, lamivudine and abacavir or tenofovir disoproxil, lamivudine and didanosine. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiviral therapy, including tenofovir disoproxil. In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, 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 antiretroviral therapy. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis joroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Bone Effects:

Bone toxicities including a reduction in bone mineral density (BMD) have been observed in studies in three animal species (see Section 5.3 PRECLINICAL SAFETY DATA: Animal Toxicology). Clinically relevant bone abnormalities have not been seen in long term clinical studies in adults (>3 years).

Bone abnormalities may be associated with proximal renal tubulopathy (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Post-Marketing Surveillance). If bone abnormalities are suspected during therapy then appropriate consultation should be obtained.

There is limited clinical experience with tenofovir in paediatric patients. In a clinical study of HIV-1 infected paediatric patients 12 years of age and older (Study 0321), bone effects were similar to adult patients. Under normal circumstances BMD increases rapidly in this age group. In this study, the mean rate of bone gain was less in the tenofovir-treated group compared to the placebo group. Six tenofovir treated patients and one placebo treated patient had significant (>4%) lumbar spine BMD loss in 48 weeks. Markers of bone turnover in tenofovir-treated paediatric patients 12 years of age and older suggest increased bone turnover, consistent with the bone effects observed in adults. The effects of tenofovir-associated changes in BMD and biochemical markers on long-term bone health and fracture risk are unknown. In a clinical study (Study 115) conducted in paediatric subjects 12 years of age and older with chronic HBV infection, both the tenofovir and placebo treatment arms experienced an overall increase in mean spine BMD, as expected for an adolescent population. The percent increase from baseline in spine BMD in tenofovir-treated subjects was less than the increase observed in placebo-treated subjects. During the study, three subjects in the tenofovir group and two subjects in the placebo group had a decrease of more than 4% in lumbar spine BMD.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

Tenofovir is excreted renally. Coadministration of TENOFOVIR DISOPROXIL VIATRIS with medicinal products that decrease or compete for renal clearance may increase serum concentrations of tenofovir.

Tenofovir disoproxil has been evaluated in healthy volunteers in combination with abacavir, didanosine, efavirenz, emtricitabine (EMTRIVA), entecavir, indinavir, lamivudine, (3TC), ledipasvir/sofosbuvir, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, rifampicin, saquinavir/ritonavir, sofosbuvir and tacrolimus (refer to Tables 2 and 3).

When administered with tenofovir disoproxil (as fumarate), Cmax and AUC of didanosine administered as either the buffered or enteric-coated formulation at a dose of 400 mg daily increased significantly (see Table 4). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis and neuropathy. Suppression of CD4 cell counts has been observed in patients receiving tenofovir disoproxil with didanosine at a dose of 400 mg daily. In patients weighing ≥60kg, the didanosine dose should be reduced to 250 mg when it is co-administered with tenofovir. Data are not available to recommend a dose adjustment of didanosine for adult or paediatric patients weighing <60kg. When co-administered, TENOFOVIR DISOPROXIL VIATRIS and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Co-administration of didanosine buffered tablet formulation with TENOFOVIR DISOPROXIL VIATRIS should be under fasted conditions. **Co-administration of TENOFOVIR DISOPROXIL VIATRIS and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.**

Tenofovir disoproxil affects the pharmacokinetics of atazanavir. TENOFOVIR DISOPROXIL VIATRIS should only be administered with boosted atazanavir (ATZ 300mg/RTV 100mg). The safety and efficacy of this regimen has been substantiated over 48 weeks in a clinical study.

Coadministration of tenofovir disoproxil and HARVONI (ledipasvir/sofosbuvir), EPCLUSA (sofosbuvir/velpatasvir), or VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) has been shown to increase

tenofovir exposure. Patients receiving TENOFOVIR DISOPROXIL VIATRIS concomitantly with HARVONI, EPCLUSA or VOSEVI should be monitored for adverse reactions associated with tenofovir.

Since tenofovir is primarily eliminated by the kidneys, co-administration of TENOFOVIR DISOPROXIL VIATRIS with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs.

Drug Interactions

At concentrations substantially higher (~ 300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP450 isoforms: CYP3A4, CYP2D6, CYP2C9 or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. 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 (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of TENOFOVIR DISOPROXIL VIATRIS with drugs that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the co-administered drug, due to competition for this elimination pathway. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

Tenofovir disoproxil has been evaluated in healthy volunteers in combination with abacavir, didanosine, efavirenz, emtricitabine (Emtriva®), entecavir, indinavir, lamivudine (3TC), ledipasvir/sofosbuvir, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin saquinavir/ritonavir, sofosbuvir and tacrolimus. Tables 2 and 3 summarise pharmacokinetic effects of co-administered drug on tenofovir pharmacokinetics and effects of tenofovir on the pharmacokinetics of co-administered drug.

When unboosted atazanavir (400 mg) was co-administered with tenofovir disoproxil, atazanavir increased tenofovir Cmax by 14% and AUC by 24%. Similarly, lopinavir (400 mg)/ritonavir (100 mg) increased tenofovir AUC by 32%.

Co-administration of tenofovir disoproxil with didanosine and atazanavir results in changes in the pharmacokinetics of didanosine and atazanavir that may be of clinical significance. Table 4 summarises the drug interaction between tenofovir and didanosine. When administered with multiple doses of tenofovir disoproxil (as fumarate), the Cmax and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil (as fumarate), systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Table 2. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir disoproxil (as fumarate)[1] in the Presence of the Co-administered Drug

Co-administered Drug	**Dose of Co-administered Drug (mg)**	**N**	**% Change of Tenofovir DF Pharmacokinetic Parameters[2] (90% CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	⇔	⇔	NC
Atazanavir[3]	400 once daily x 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28)	↑22 (↑15 to ↑30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)[4]	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily x	29	⇔	⇔	⇔

	14 days				
Emtricitabine (Emtriva)	200 once daily x 7 days	17	⇔	⇔	⇔
Entecavir	1 mg once daily x 10 days	28	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑14 (↓3 to ↑33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Ledipasvir/ Sofosbuvir[5,6]	90/400 once daily x 10 days	24	↑47 (↑37 to ↑58)	↑ 35 (↑29 to ↑42)	↑47 (↑38 to ↑57)
Ledipasvir/ Sofosbuvir[5,7]		23	↑64 (↑54 to ↑74)	↑50 (↑42 to ↑59)	↑59 (↑49 to ↑70)
Ledipasvir/ Sofosbuvir[8]		15	↑79 (↑56 to ↑104)	↑98 (↑77 to ↑123)	↑163 (↑132 to ↑197)
Ledipasvir/ Sofosbuvir[9]		14	↑32 (↑25 to ↑39)	↑40 (↑31 to ↑50)	↑91 (↑74 to ↑110)
Ledipasvir/ Sofosbuvir[10]		29	↑61 (↑51 to ↑72)	↑65 (↑59 to ↑71)	↑115 (↑105 to ↑126)
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	⇔	↑32 (↑26 to ↑38)	↑51 (↑32 to ↑66)
Methadone[11]	40-110 once daily x 14 days[12]	13	⇔	⇔	⇔
Nelfinavir	1250 twice daily x 14 days	29	⇔	⇔	⇔
Oral Contraceptives[13]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen®) Once daily x 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NC
Saquinavir/ Ritonavir	1000/100 twice daily x 14 days	35	⇔	⇔	↑23 (↑16 to ↑30)
Sofosbuvir[14]	400 once daily	16	↑25 (↑8 to ↑45)	⇔	⇔
Sofosbuvir/ Velpatasvir[15]	400/100 once daily	24	↑55 (↑43 to ↑68)	↑30 (↑24 to ↑36)	↑39 (↑31 to ↑48)
Sofosbuvir/ Velpatasvir[16]	400/100 once daily	29	↑55 (↑45 to ↑66)	↑39 (↑33 to ↑44)	↑52 (↑45 to ↑59)
Sofosbuvir/ Velpatasvir[17]	400/100 once daily	15	↑77 (↑53 to ↑104)	↑81 (↑68 to ↑94)	↑121 (↑100 to ↑143)
Sofosbuvir/ Velpatasvir[18]	400/100 once daily	24	↑36 (↑25 to ↑47)	↑35 (↑29 to ↑42)	↑45 (↑39 to ↑51)
Sofosbuvir/	400/100 once	24	↑44	↑40	↑84

Velpatasvir[19]	daily		(↑33 to ↑55)	(↑34 to ↑46)	(↑76 to ↑92)
Sofosbuvir/ Velpatasvir[20]	400/100 once daily	30	↑46 (↑39 to ↑54)	↑40 (↑34 to ↑45)	↑70 (↑61 to ↑79)
Sofosbuvir/ velpatasvir/ voxilaprevir[21]	400/100/100 + voxilaprevir[22] 100 once daily	29	↑48 (↑36 to ↑61)	↑39 (↑32 to ↑46)	↑47 (↑38 to ↑56)
Tacrolimus [23]	0.05 mg/kg twice daily x 7 days	21	↑13 (↑1 to ↑27)	⇔	⇔

1. Subjects received tenofovir disoproxil fumarate (DF) 300 mg once daily.
2. Increase = ↑; Decrease = ↓; No Effect = ; NC = Not Calculated.
3. REYATAZTM Prescribing Information (Bristol-Myers Squibb).
4. Includes 4 subjects weighing <60 kg receiving ddI 250 mg.
5. Data generated from simultaneous dosing with HARVONI® (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provide similar results.
6. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.
7. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
8. Study conducted with ATRIPLA (tenofovir DF/emtricitabine/efavirenz) coadministered with HARVONI.
9. Study conducted with EVIPLERA (tenofovir DF/emtricitabine/rilpivirine) coadministered with HARVONI.
10. Study conducted with TRUVADA (emtricitabine/tenofovir DF) + dolutegravir coadministered with HARVONI.
11. R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir DF.
12. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
13. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir DF.
14. Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).
15. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.
16. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
17. Study conducted with ATRIPLA coadministered with EPCLUSA (sofosbuvir/velpatasvir).
18. Study conducted with STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir DF) coadministered with EPCLUSA.
19. Study conducted with EVIPLERA coadministered with EPCLUSA.
20. Administered as raltegravir + emtricitabine/tenofovir DF.
21. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
22. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.
23. Subjects received tenofovir DF 300 mg once daily as the combination product TRUVADA.

Following multiple dosing to HIV- and HBV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant drug interactions between these agents and tenofovir. In a study conducted in healthy volunteers dosed with a single 600 mg dose of ribavirin, no clinically significant drug interactions were observed between tenofovir disoproxil (as fumarate) and ribavirin.

Table 3. Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of tenofovir disoproxil (as fumarate)

Co-administered Drug	**Dose of Co-administered Drug (mg)**	**N**	**% Change of Co-administered Drug Pharmacokinetic Parameters[1] (90% CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑12 (↓1 to ↑26)	⇔	NA
Atazanavir[2]	400 once daily x 14 days	34	↓21 (↓27 to ↓14)	↓25 (↓30 to ↓19)	↓40 (↓48 to ↓32)
Atazanavir[2]	Atazanavir/Ritonavir[3] 300/100 once daily X 42 days	10	↓28 (↓50 to ↑5)[3]	↓25 (↓42 to ↓3)[3]	↓23 (↓46 to ↑10)[3]
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	↑20

(Emtriva)					(↑12 to ↑29)
Entecavir	1 mg once daily x 10 days	28	⇔	↑13 (↓11 to ↑15)	⇔
Indinavir	800 three times daily x 7 days	12	↓11 (↓30 to ↑12)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	↓24 (↓34 to↓12)	⇔	⇔
Ledipasvir Sofosbuvir GS-331007[4]	Ledipasvir/Sofosbuvir 90/400 once daily x 10 days[5, 6]	24	↑68 (↑54 to ↑84)	↑96 (↑74 to ↑121)	↑118 (↑91 to ↑150)
			⇔	⇔	N/A
			↑17 (↑12 to ↑23)	↑31 (↑25 to ↑36)	↑42 (↑34 to↑49)
Ledipasvir Sofosbuvir GS-331007[4]	Ledipasvir/Sofosbuvir 90/400 once daily x 10 days[5,7]	23	⇔	⇔	⇔
			↓37 (↓48 to ↓25)	↓27 (↓35 to ↓18)	N/A
			⇔	⇔	⇔
Ledipasvir Sofosbuvir GS-331007[4]	Ledipasvir/Sofosbuvir 90/400 once daily x 10 days[8]	15	↓34 (↓41 to ↓25)	↓34 (↓41 to ↓25)	↓34 (↓43 to ↓24)
			⇔	⇔	N/A
			⇔	⇔	⇔
Ledipasvir Sofosbuvir GS-331007[4]	Ledipasvir/Sofosbuvir 90/400 once daily x 10 days[9]	14	⇔	⇔	⇔
			⇔	⇔	N/A
			⇔	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Methadone[10]	40-110 once daily x 14 days[11]	13	⇔	⇔	⇔
Nelfinavir M8 Metabolite	1250 twice daily x 14 days	29	⇔ ⇔	⇔ ⇔	⇔ ⇔
Oral Contraceptives[12]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen®) Once daily x 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
Saquinavir Ritonavir	Saquinavir/ Ritonavir 1000/100 twice daily x 14 days	32	↑22 (↑6 to ↑41) ⇔	↑29[13] (↑12 to ↑48) ⇔	↑47[13] (↑23 to ↑76) ↑23 (↑3 to ↑46)
Sofosbuvir GS-331007[4]	Sofosbuvir 400 once daily x 10 days[14]	16	↓19 (↓40 to ↑10)	⇔	N/A
			↓23 (↓30 to ↓16)	⇔	N/A
Tacrolimus[15]	0.05 mg/kg twice daily x 7 days	21	⇔	⇔	⇔

1. Increase = ↑; Decrease = ↓; No Effect = □; NA = Not Applicable
2. REYATAZ™ Prescribing Information (Bristol-Myers Squibb)

3. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and Cmin values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone (REYATAZ™ March 2004 United States Package Insert)
4. The predominant circulating nucleoside metabolite of sofosbuvir
5. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provide similar results
6. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF
7. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF
8. Study conducted with ATRIPLA (tenofovir DF/emtricitabine/efavirenz) coadministered with HARVONI
9. Study conducted with EVIPLERA (tenofovir DF/emtricitabine/rilpivirine) coadministered with HARVONI
10. R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir DF.
11. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
12. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir DF.
13. Increases in AUC and Cmin are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.
14. Study conducted with ATRIPLA coadministered with SOVALDI (sofosbuvir)
15. Subjects received tenofovir DF 300 mg once daily as the combination product TRUVADA.

Table 4. Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of Tenofovir disoproxil (as fumarate)

Didanosine[1] Dose (mg)/ Method of Administration[2]	**Tenofovir DF Method of Administration[2]**	**N**	**% Difference (90% CI) vs. Didanosine 400 mg alone, Fasted[3]**	
			C_{max}	**AUC**
Buffered tablets				
400 once daily[4] x 7 days	Fasted 1 hour after didanosine	14	↑28 (↑ 11 to ↑ 48)	↑44 (↑ 31 to ↑ 59)
Enteric coated capsules				
400 once, fasted	With food, 2 hr after didanosine	26	↑48 (↑ 25 to ↑ 76)	↑48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑64 (↑ 41 to ↑ 89)	↑60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hr after didanosine	28	↓10 (↓ 22 to ↑ 3)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

1. See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE regarding use of didanosine with tenofovir.
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. Increase = ↑; Decrease = ↓; No Difference = □
4. Includes 4 subjects weighing <60kg receiving ddI 250mg

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There are limited clinical data with respect to the effects of tenofovir disoproxil on fertility. Animal studies do not indicate harmful effects of tenofovir disoproxil on fertility (See Section 5.3 PRECLINICAL SAFETY DATA).

Use in Pregnancy

Pregnancy Category: B3

Category B3: Tenofovir disoproxil (as fumarate) (300 mg given once daily to mothers) in combination with standard of care (administration of hepatitis B immunoglobulin and hepatitis B vaccine in infants) was evaluated for the prevention of mother to child transmission (MTCT) of HBV in three controlled, clinical studies in women who were pregnant and chronically infected with HBV. In these studies, Tenofovir disoproxil (as fumarate) was administered to a total of 327 HBeAg-positive pregnant women from 28 to 32 weeks gestation through 1 to 2 months postpartum. Patients were followed up to 12 months after delivery; there were no new safety findings in mothers

compared with the known safety profile of Tenofovir disoproxil (as fumarate) in HBV-infected adults and there were no clinically relevant safety findings in the infants.

Animal studies do not indicate harmful effects of tenofovir disoproxil fumarate with respect to pregnancy (see section 5.3 PRECLINICAL SAFETY DATA). Because animal reproduction studies are not always predictive of human response, TENOFOVIR DISOPROXIL VIATRIS should be used during pregnancy only if clearly needed.

Use in Lactation

In humans, samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk at low concentrations (estimated neonatal concentrations 128 to 266 times lower than the tenofovir IC_{50} (50% maximal inhibitory concentration). Tenofovir associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir are unknown. It is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

From Clinical Studies

Clinical Trials in Adult Patients with HIV Infection

More than 12,000 patients have been treated with tenofovir disoproxil alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in Phase I-III clinical trials and expanded access studies. A total of 1,544 patients have received tenofovir disoproxil (as fumarate) 300 mg once daily in Phase I-III clinical trials; over 11,000 patients have received tenofovir disoproxil in expanded access studies.

Treatment-Experienced Adult Patients

Treatment-Emergent Adverse Events:

The most common adverse events that occurred in patients receiving tenofovir disoproxil with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhoea, vomiting and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse events (Study 907).

A summary of treatment-emergent adverse events that occurred during the first 48 weeks of Study 907 is provided in Table 5 (below).

Table 5. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 907 (0–48 weeks)

	TENOFOVIR DISOPROXIL (N=368) (Week	**Placebo (N=182) (Week 0–24)**	**TENOFOVIR DISOPROXIL (N=368)**	**Placebo Crossover to TENOFOVIR DISOPROXIL (N=170)**

	0–24) %	%	(Week 0–48) %	(Week 24–48) %
Body as a whole				
Asthenia	7	6	11	1
Pain	7	7	12	4
Headache	5	5	8	2
Abdominal Pain	4	3	7	6
Back Pain	3	3	4	2
Chest Pain	3	1	3	2
Fever	2	2	4	2
Digestive System				
Diarrhoea	11	10	16	11
Nausea	8	5	11	7
Vomiting	4	1	7	5
Anorexia	3	2	4	1
Dyspepsia	3	2	4	2
Flatulence	3	1	4	1
Respiratory				
Pneumonia	2	0	3	2
Nervous System				
Depression	4	3	8	4
Insomnia	3	2	4	4
Peripheral Neuropathy[1]	3	3	5	2
Dizziness	1	3	3	1
Skin and Appendage				
Rash Event[2]	5	4	7	1
Sweating	3	2	3	1
Musculoskeletal				
Myalgia	3	3	4	1
Metabolic				
Weight Loss	2	1	4	2

1. Peripheral neuropathy includes peripheral neuritis and neuropathy
2. Rash event includes, rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash

Laboratory Abnormalities

Laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 6 below.

Table 6. Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% of TENOFOVIR DISOPROXIL-Treated Patients Study 907 (0-48 weeks)

	TENOFOVIR DISOPROXIL	Placebo (N=182)	TENOFOVIR DISOPROXIL	Placebo Crossover to TENOFOVIR DISOPROXIL

	(N=368) (Week 0–24) %	(Week 0–24) %	(N=368) (Week 0–48) %	(N=170) (Week 24–48) %
Any ≥ Grade 3 Laboratory Abnormality	25	38	35	34
Triglycerides (>750 mg/dL)	8	13	11	9
Creatine Kinase (M: >990U/L) (F: >845 U/L)	7	14	12	12
Serum Amylase (> 175 U/L)	6	7	7	6
Urine Glucose (≥3+)	3	3	3	2
AST (M: >180 U/L) (F: >170 U/L)	3	3	4	5
ALT (M: >215 U/L) (F: >170 U/L)	2	2	4	5
Serum Glucose (>250 U/L)	2	4	3	3
Neutrophils (<750 mg/dL)	1	1	2	1

Treatment-Naïve Adult Patients

Treatment-Emergent Adverse Events:

In a double-blind active controlled study in which 600 treatment-naïve patients received tenofovir disoproxil (N=299) or d4T (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) the adverse reactions seen were generally consistent, with the addition of dizziness, with those seen in treatment-experienced patients (Table 7).

Mild adverse events (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhoea and nausea.

Table 7. Selected Treatment-Emergent Adverse Events (Grades 2-4) Reported in ⩾ 5% in Any Treatment Group in Study 903 (0-144 weeks)

	TENOFOVIR DISOPROXIL+3TC+EFV (%)	D4T+3TC+EFV (%)
	N=299	N=301
<u>Body as a Whole</u>		
Headache	14	17
Pain	13	12
Back Pain	9	8
Fever	8	7
Abdominal Pain	7	12
Asthenia	6	7
<u>Digestive System</u>		
Diarrhoea	11	13
Nausea	8	9
Vomiting	5	9
Dyspepsia	4	5

Metabolic Disorders Lipodystrophy	1	8
Musculoskeletal Arthralgia	5	7
Myalgia	3	5
Nervous System Depression	11	10
Anxiety	6	6
Insomnia	5	8
Dizziness	3	6
Peripheral neuropathy[1]	1	5
Respiratory Pneumonia	5	5
Skin and Appendages Rash Event[2]	18	12

1. Peripheral neuropathy includes peripheral neuritis and neuropathy
2. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash

Laboratory Abnormalities:

With the exception of triglyceride elevations that were more common in the d4T group (14%) compared with tenofovir disoproxil (3%), laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil and d4T treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 8.

Table 8. Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% of TENOFOVIR DISOPROXIL-Treated Patients in Study 903 (0–144 weeks)

	TENOFOVIR DISOPROXIL+3TC+EFV (%)	**D4T+3TC+EFV (%)**
	N=299	**N=301**
Any ≥ Grade 3 Laboratory Abnormality	36	42
Creatine Kinase (M: > 990 U/L) (F: > 845 U/L)	12	12
Serum Amylase (>175 U/L)	9	8
AST (M: >180 U/L) (F: >170 U/L)	5	7
ALT (M: >215 U/L) (F: >170 U/L)	4	5
Haematuria (>100 RBC/HPF)	7	7
Neutrophil (<750/mm^3)	3	1
Triglyceride (>750 mg/dL)	3	13

Study 934 - Treatment Emergent Adverse Events:

Study 934 was an open-label active controlled study in which 511 antiretroviral-naïve patients received either tenofovir disoproxil + EMTRIVA administered in combination with efavirenz (n=257) or Combivir (lamivudine/zidovudine) administered in combination with efavirenz (n=254). Adverse events observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment naïve patients (Table 9). Adverse events leading to study drug discontinuation occurred in significantly smaller

number of patients in the TRUVADA (tenofovir disoproxil/emtricitabine) group compared to the Combivir group (5% vs 11%, p=0.010). The most frequently occurring adverse event leading to study drug discontinuation was anaemia (including decreased haemoglobin), no patient in the TRUVADA group and 6% of patients in the Combivir group.

Table 9. Frequency of Adverse Reactions to EMTRIVA and/or TENOFOVIR DISOPROXIL (Grade 2‑ 4) Occurring in ≥ 3% of Patients Receiving EMTRIVA and TENOFOVIR DISOPROXIL (or TRUVADA) in Study 934 (0-144 Weeks)[1]

Adverse Reaction	TRUVADA[2] +EFV N=257	Combivir + EFV N=254
Gastrointestinal Disorders		
Diarrhoea	9%	5%
Nausea	9%	7%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Insomnia	5%	7%
Abnormal Dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

1. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
2. Patients received tenofovir disoproxil + EMTRIVA up to week 96 and switched to TRUVADA from week 96 to 144.

Laboratory Abnormalities:

Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 10).

Table 10. Grade 3/4 Laboratory Abnormalities Reported in >1% of Patients in Either Treatment Group, Study 934 (0–144 weeks)

	TRUVADA[1] + EFV N=254	Combivir + EFV N=251
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hyperglycaemia (>250 mg/dL)	2%	1%
Haematuria (>75 RBC/HPF)	3%	2%
Neutrophil (<750/mm^3)	3%	5%
Triglyceride (>750 mg/dL)	5%	3%

Haemoglobin (<7.0 g/dL)	0%	2%

1. Patients received tenofovir disoproxil+ EMTRIVA up to week 96 and switched to TRUVADA from week 96 to 144.

Clinical Trials in Paediatric Patients 12 Years of Age and Older with HIV Infection:

Assessment of adverse reactions is based on one randomised study (study 321) in 87 HIV infected paediatric patients (12 to 18 years of age) who received treatment with tenofovir disoproxil (n=45) or placebo (n=42) in combination with other antiretroviral agents for 48 weeks. The adverse reactions observed in paediatric patients 12 years of age and older who received treatment with tenofovir disoproxil were consistent with those observed in clinical studies in adults. Bone effects similar to those seen in adults were observed in this study (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Clinical Trials in Adult Patients with Hepatitis B:

Assessment of adverse reactions is based on experience in two double-blind comparative controlled studies (0102 and 0103) in which 641 patients with chronic hepatitis B and compensated liver disease received treatment with tenofovir disoproxil (as fumarate) 300 mg daily (n=426) or HEPSERA 10 mg daily (n=215) for 48 weeks (see Table 11).

The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and frequency.

Gastrointestinal disorders: Common: nausea

Table 11. Most Frequent (>5%) Treatment-Emergent Adverse Events of Any Severity (Integrated RAT analysis set; 48-week Data from Studies 102 and 103)

AEs by Preferred Term[a] (n, %)[b]	**Overall TDF (N=426)**	**Overall ADV (N=215)**
Any Adverse Event	317 (74.4%)	158 (73.5%)
Headache	55 (12.9%)	30 (14.0%)
Nasopharyngitis	42 (9.9%)	24 (11.2%)
Nausea	40 (9.4%)	6 (2.8%)
Fatigue	36 (8.5%)	16 (7.4%)
Abdominal Pain Upper	30 (7.0%)	11 (5.1%)
Back Pain	30 (7.0%)	10 (4.7%)
Diarrhoea	28 (6.6%)	11 (5.1%)
Dizziness	24 (5.6%)	7 (3.3%)
Procedural Pain	16 (3.8%)	12 (5.6%)
Pharyngolaryngeal Pain	15 (3.5%)	11 (5.1%)
Upper Respiratory Tract Infection	13 (3.1%)	11 (5.1%)

[a] Events coded using MedDRA dictionary version 9.1.

[b] Subjects are counted once only for each system organ class and preferred term, counting the most severe occurrence

Laboratory Abnormalities:

A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 12.

Table 12. Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Tenofovir disoproxil-Treated Patients in Studies 0102 and 0103 (0-48 weeks)

	TENOFOVIR DISOPROXIL	**HEPSERA (N=215)**

	(N=426)	
Any ≥ Grade 3 Laboratory Abnormality	19%	13%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	2%	3%
Serum Kinase (>175 U/L)	4%	1%
Glycosuria (≥ 3+)	3%	< 1%
AST (M: >180 U/L; F: >170 U/L)	4%	4%
ALT (M: >215 U/L; F: >170 U/L)	10%	6%

Treatment beyond 48 weeks: The adverse reactions observed with continued treatment for 384 weeks were consistent with the safety profile of tenofovir disoproxil. Grade 3/4 laboratory abnormalities were similar in nature and frequency in patients continuing treatment for up to 288 weeks in these studies.

Nucleos(t)ide-Experienced Patients: No new adverse reactions to tenofovir disoproxil were identified in those patients in studies 0102, 0103 and 0106 and 0121 who had been previously treated with HEPSERA, lamivudine or other nucleoside analogs (n=493).

Patients with Decompensated Liver Disease: No new adverse reactions to tenofovir disoproxil were identified from a double-blind active-controlled study (0108) in which patients with decompensated liver disease received treatment with tenofovir disoproxil (n=45) for 48 weeks. Among the 45 subjects receiving tenofovir disoproxil, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the study due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus < 2mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score ≥ 10 and MELD score ≥ 14 at entry) developed renal failure. Because both tenofovir and decompensated liver disease may have an impact on renal function, the contribution of tenofovir to renal impairment in this population is difficult to ascertain.

One of 45 subjects experienced an on-treatment hepatic flare during the 48 Week study.

At week 168, in this population of patients with decompensated liver disease, the rate of death was 13% (6 of 45) in the tenofovir disoproxil group, 11% (5 of 45) in the emtricitabine plus tenofovir disoproxil group and 14% (3 of 22) in the entecavir group. The rate of serious hepatocellular carcinoma was 18% (8 of 45) in the tenofovir disoproxil group, 7% (3 of 45) in the emtricitabine plus tenofovir disoproxil group and 9% (2 of 22) in the entecavir group. The rate of serious ascites, which was experienced in 7% (3 of 45) in the tenofovir disoproxil group, 7% (3 of 45) in the emtricitabine plus tenofovir disoproxil group and 5% (1 of 22) in the entecavir group. The rate of serious hepatic encephalopathy was 7% (3/45) in the tenofovir disoproxil group, 2% (1 of 45) in the emtricitabine plus tenofovir disoproxil group, and 9% (2 of 22) in the entecavir group (see Section 5.1 PHARMACODYNAMIC PROPERTIES: Clinical trials).

Clinical Trials in Paediatric Patients 12 Years of Age and Older with HBV Infection:

Assessment of adverse reactions is based on one randomised study (study 0115) in 106 paediatric patients (12 to < 18 years of age) infected with chronic hepatitis B receiving treatment with tenofovir disoproxil (n=52) or placebo (n=54) for 72 weeks. The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil were consistent with those observed in clinical studies in adults (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Post Marketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of tenofovir disoproxil. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Immune system disorders

Allergic reaction (including angioedema), autoimmune hepatitis (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Immune Reconstitution Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to infectious pathogens (active or inactive) may arise (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Metabolism and nutrition disorders

Hypokalaemia, hypophosphataemia, lactic acidosis

Respiratory, thoracis, and mediastinal disorders

Dyspnoea

Gastrointestinal disorders

Increased amylase, abdominal pain, pancreatitis

Hepatobiliary disorders

Hepatic steatosis, increased liver enzymes (most commonly AST, ALT, gamma GT), hepatitis

Skin and subcutaneous tissue disorders

Rash

Musculoskeletal and connective tissue disorders

Rhabdomyolysis, muscular weakness, myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures)

Renal and urinary disorders

Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal renal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases).

General disorders and administrations site conditions

Asthenia

Reactions as a consequence of Proximal Renal Tubulopathy:

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy, hypophosphataemia. These events are not considered to be causally associated with tenofovir disoproxil therapy in the absence of proximal renal tubulopathy.

In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adverse reactions attendant to class: Nephrotoxicity (elevation in serum creatinine and urine protein, and decrease in serum phosphorus) is the dose-limiting toxicity associated with other nucleotide analogues (cidofovir and high doses of adefovir dipivoxil evaluated for HIV disease (60 mg and 120 mg)).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Clinical experience of doses higher than the therapeutic dose of tenofovir disoproxil (as fumarate) 300 mg is available from two studies. In one study, intravenous tenofovir disoproxil (as fumarate), equivalent to 16.7 mg/kg/day of tenofovir disoproxil (as fumarate), was administered daily for 7 days. In the second study, 600 mg of tenofovir disoproxil (as fumarate) was administered to patients orally for 28 days.

No unexpected or severe adverse reactions were reported in either study. The effects of higher doses are not known.

If overdose occurs the patient must be monitored for evidence of toxicity (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), and standard supportive treatment applied as necessary.

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil (as fumarate), a four-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Tenofovir disoproxil maleate is a salt of an oral prodrug of tenofovir, a nucleoside monophosphate (nucleotide) analogue and obligate chain terminator with activity against HIV reverse transcriptase and HBV polymerase.

Tenofovir is converted to the active metabolite, tenofovir diphosphate, by constitutively expressed cellular enzymes through two phosphorylation reactions. This conversion occurs in both resting and activated T cells. 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 viral polymerases 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 mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ. At concentrations of up to 300 μM, tenofovir shows no effect on the synthesis of mitochondrial DNA (human liver, skeletal muscle and renal proximal tubular epithelial cells) or lactic acid production (human liver and skeletal muscle cells) *in vitro*.

Pharmacodynamic effects

Tenofovir has *in vitro* antiviral activity against retroviruses and hepadnaviruses.

Anti-HIV-1 activity *in vitro*

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, primary monocyte/ macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentration) for tenofovir was in the range of 0.04 μM to 8.5 μM. In drug combination

studies of tenofovir with nucleoside and non-nucleoside analogue inhibitors of HIV reverse transcriptase, and protease inhibitors, additive to synergistic effects were observed. In addition, tenofovir has also been shown to be active *in vitro* against HIV-2, with similar potency as observed against HIV-1.

Tenofovir shows activity within three fold of wild-type IC_{50} against recombinant HIV-1 expressing didanosine resistance (L74V), zalcitabine resistance (T69D), or multinucleoside drug resistance (Q151M complex) mutations in reverse transcriptase. Tenofovir shows slightly increased activity against HIV-1 expressing the abacavir/lamivudine resistance mutation M184V. The activity of tenofovir against HIV-1 strains with thymidine analog-associated mutations (thymidine-associated mutations) appears to depend on the type and number of these resistance mutations. In the presence of mutation T215Y, a twofold increase of the IC_{50} was observed. In 10 samples which had multiple thymidine-associated mutations (mean 3.4), a mean 3.7-fold increase of the IC_{50} was observed (range 0.8 to 8.4). There are insufficient data at this time to correlate specific thymidine-associated mutation patterns with reduced susceptibility to tenofovir.

Multinucleoside resistant HIV-1 with T69S double insertions have reduced susceptibility to tenofovir (IC_{50} >10-fold compared with wild type). Tenofovir shows activity against non-nucleoside reverse transcriptase inhibitor resistant HIV-1 with K103N or Y181C mutations. Cross-resistance to protease inhibitor resistance mutations is not expected due to the different viral enzymes targeted.

Strains of HIV-1 with reduced susceptibility to tenofovir have been selected *in vitro*. The selected viruses express a K65R mutation in RT and showed 3 to 4-fold reduced susceptibility to tenofovir. The K65R mutation in RT can also be selected by zalcitabine, didanosine, and abacavir, and causes reduced susceptibility to zalcitabine, didanosine, stavudine (d4T), abacavir, and lamivudine (14-, 4-, 2-, 3-, and 25-fold, respectively). In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility tenofovir. This substitution is also associated with reduced susceptibility to abacavir, didanosine, emtricitabine and lamivudine.

Anti-Hepatitis B Virus Activity *In Vitro*

The *in vitro* antiviral activity of tenofovir against laboratory strains and clinical isolates of HBV was assessed in HepG2 cells. The EC_{50} values for tenofovir were in the range 0.06 to 1.5 μM. Tenofovir diphosphate inhibits recombinant HBV polymerase with a Ki (inhibition constant) of 0.18 μM. In *in vitro* drug combination studies of tenofovir with nucleoside anti-HBV reverse transcriptase inhibitors lamivudine, telbivudine and entecavir, additive anti-HBV activity was observed. Additive to slight synergistic effects were observed with the combination of tenofovir and emtricitabine.

Clinical Trials

Clinical efficacy in HIV Infection:

The demonstration of benefit of tenofovir is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of tenofovir disoproxil in treatment-naïve adults and in treatment experienced adults.

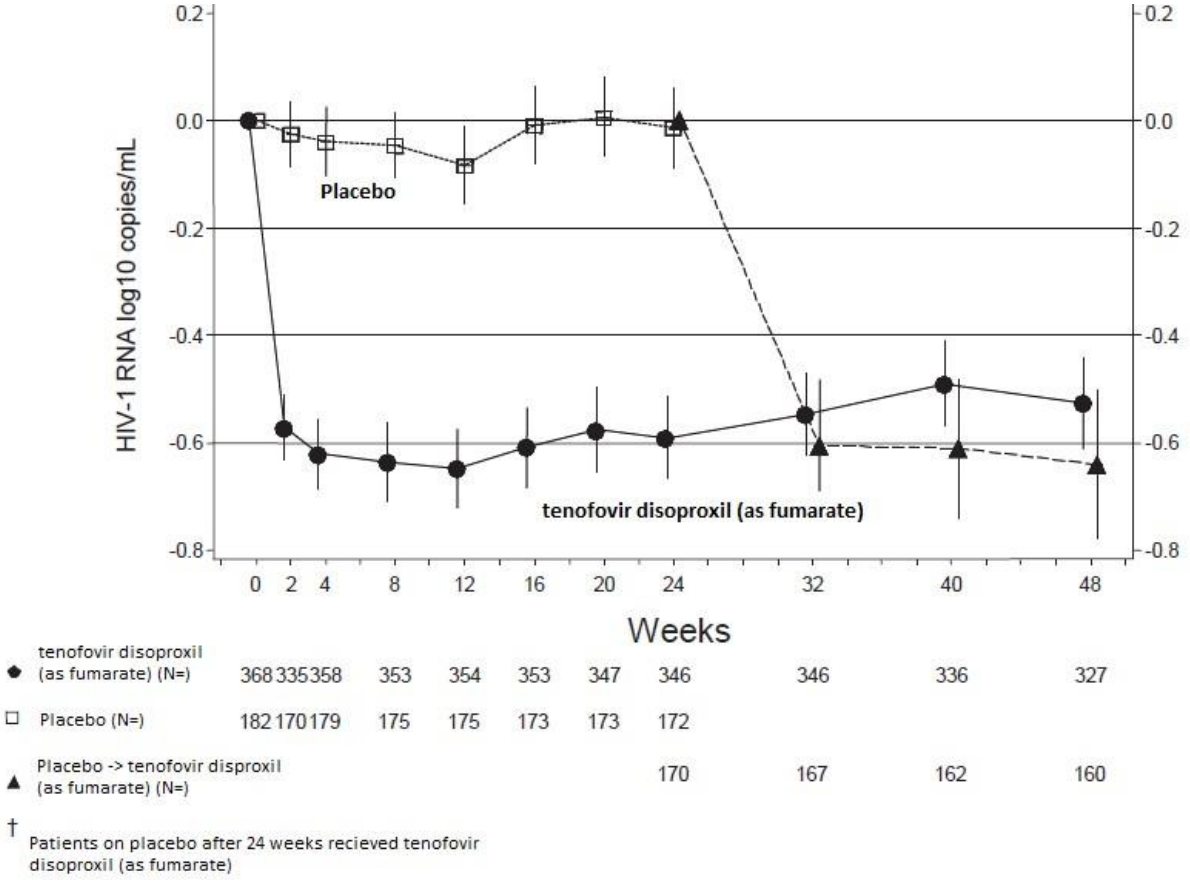
Treatment – Experienced Adult Patients

Study 907: Tenofovir disoproxil + Standard Background Therapy (SBT) Compared to Placebo + SBT

Study 907 was a 24 week, double-blind placebo-controlled multicentre study of tenofovir disoproxil added to a stable background regimen of antiretroviral agents in 550 treatment-experienced patients. After 24 weeks of blinded study treatment, all patients continuing on study were offered open-label tenofovir disoproxil for an additional 24 weeks. Patients had a mean baseline CD4 cell count of 427 cells/mm^3 (range 23–1385), median baseline plasma HIV-1 RNA of 2340 (range 50–75,000) copies/mL, and mean duration of prior HIV-1 treatment was 5.4 years. Mean age of the patients was 42 years, 85% were male and 69% were Caucasian, 17% Black and 12% Hispanic.

Changes from baseline in log10 copies/mL plasma HIV-1 RNA levels over time up to week 48 are presented below in Figure 1.

Figure 1 Mean Change from Baseline in Plasma HIV-1 RNA (log10 copies/mL) Through Week 48: Study 907 (All Available Data)†



The percent of patients with HIV-1 RNA <400 copies/mL and outcomes of patients through 48 weeks are summarised in Table 13.

Table 13. Outcomes of Randomised Treatment (Study 907)

Outcomes	**0-24 weeks**		**0-48 weeks**	**24-48 weeks**
	TENOFOVIR DISOPROXIL (N=368) % (95% CI)	**Placebo (N=182) % (95% CI)**	**TENOFOVIR DISOPROXIL (N=368) %**	**Placebo Crossover to TENOFOVIR DISOPROXIL (N=170) %**
HIV-1 RNA <400 copies/mL[1]	40%[4] (35% to 45%)	11%[4] (6% to 16%)	28%	30%
Virologic failure[2]	53%	84%	61%	64%
Discontinued due to adverse event	3%	3%	5%	5%
Discontinued for other reasons[3]	3%	3%	5%	1%

1. Patients with HIV-1 RNA < 400 copies/mL and no prior study drug discontinuation at Week 24 and 48 respectively
2. Patients with HIV-1 RNA ≥400 copies/mL efficacy failure or missing HIV –1 RNA at Week 24 and 48 respectively
3. Includes lost to follow up, patient withdrawal, non-compliance, protocol violation and other reasons.
4. Difference 29% $p < 0.001$

At 24 weeks of therapy, there was a higher proportion of patients in the tenofovir arm compared to the placebo arm with HIV-1 RNA <50 copies/mL (19% and 1% respectively). Mean change in absolute CD4 counts by

week 24 was +11 cells/mm^3 for tenofovir group and -5 cells/mm^3 for the placebo group. Mean change in absolute CD4 counts by week 48 was +4 cells/mm^3 for the tenofovir group.

Treatment-Experienced Paediatric Patients 12 Years of Age and Older

In study GS-US-104-0321 (study 321), 87 treatment-experienced patients 12 to <18 years of age were treated with tenofovir disoproxil (n=45) or placebo (n=42) in combination with an optimised background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm^3 and the mean baseline plasma HIV-1 RNA was 4.6 log10 copies/mL. The median $DAVG_{24}$ and $DAVG_{48}$ in plasma HIV-1 RNA were -1.58 and -1.42 log10 copies/mL for the tenofovir treatment group compared to -1.55 and -1.35 log10 copies/mL, respectively, for the placebo group at weeks 24 and 48. Overall, the trial failed to show a difference in virologic response between the two treatment groups. Subgroup analyses suggest the lack of difference in virological response may be attributable to imbalances between treatment arms in baseline viral susceptibility to tenofovir and OBR. In patients with partially active or non-active OBR (genotypic sensitivity score ≤ 1), the addition of tenofovir disoproxil or placebo resulted in a median $DAVG_{24}$ in plasma HIV RNA of -1.66 and -1.14 log10 copies/mL, respectively. Although changes in HIV-1 RNA in these highly treatment experienced patients were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of tenofovir disoproxil in paediatric patients ≥ 12 years of age who weigh ≥ 35 kg whose HIV-1 isolate is expected to be sensitive to tenofovir.

HIV-1 isolates from 43 patients who had plasma HIV-1 RNA ≥ 400 copies/mL were evaluated for tenofovir resistance-associated substitutions. One patient developed the K65R substitution by week 48.

Treatment-Naïve Adult Patients

Study 903: Tenofovir disoproxil + Lamivudine + Efavirenz Compared to Stavudine + Lamivudine + Efavirenz

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicentre study comparing tenofovir disoproxil (as fumarate) (300 mg once daily) administered in combination with lamivudine and efavirenz versus d4T, lamivudine, and efavirenz in 600 antiretroviral-naïve patients. Patients had a mean age of 36 years (range 18–64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4 cell count was 279 cells/mm^3 (range 3–956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417–5,130,000). 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/mm^3. Treatment outcomes through 144 weeks are presented in Table 14 below.

Table 14. Outcomes of Randomised Treatment (Study 903)

Outcomes	**At week 48**		**At week 144**	
	Tenofovir disoproxil + 3TC+EFV (N=299)	**d4T +3TC+EFV (N=301)**	**Tenofovir disoproxil + 3TC+EFV (N=299)**	**d4T +3TC+EFV (N=301)**
	%	**%**	**%**	**%**
Responder[1]	79[4]	82[4]	68[5]	62[5]
Virologic failure[2]	6	4	10	8
Rebound	5	3	8	7
Never suppressed	0	1	0	0
Added an antiretroviral agent	1	1	2	1
Death	<1	1	<1	2
Discontinued due to adverse event	6	6	8	13
Discontinued for other	8	7	14	15

reasons[3]				

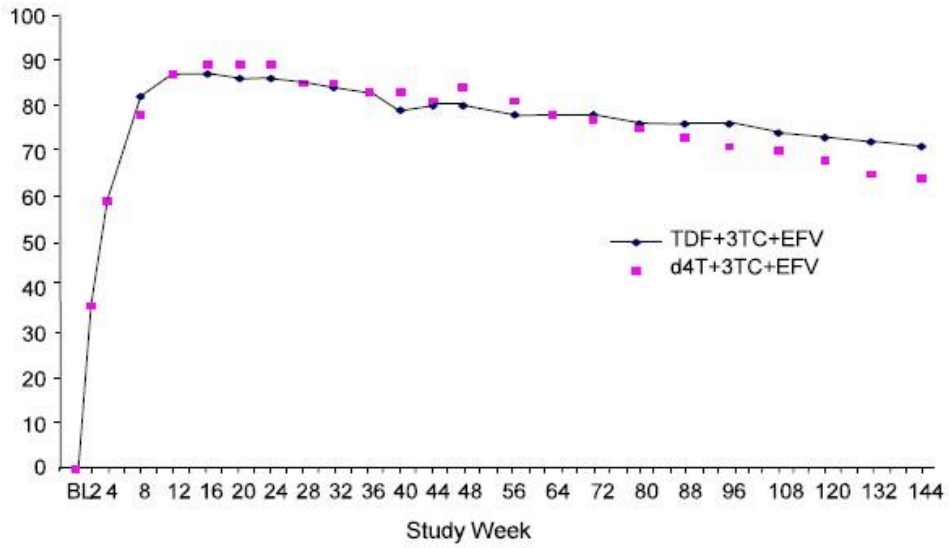
1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.
3. Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.
4. Difference -3.0% (-9.2% to 3.1%) p=0.48. The difference and confidence interval are stratum weighted on baseline HIV-1 RNA and CD4.
5. Difference 6.1% (-1.4% to 13.7%) p=0.11. The difference and confidence interval are stratum weighted on baseline HIV-1 RNA and CD4.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (≤ or >100,000 copies/mL) and CD4 cell count (< or ≥200 cells/mm^3). Through 144 weeks of therapy, 62% and 58% of patients in the tenofovir and d4T arms, respectively achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4 cell count was 263 cells/mm^3 for the tenofovir arm and 283 cells/mm^3 for the d4T arm.

The percentage of patients who achieved and maintained confirmed HIV RNA <400 using intent-to-treat analysis through 144 weeks of treatment in study 903 is presented in Figure 2 below.

Genotypic analyses of patients with virologic failure showed development of efavirenz-associated and lamivudine-associated mutations to occur most frequently and with no difference between the treatment arms. The K65R mutation occurred in 8 patients on the tenofovir arm and in 2 patients on the d4T arm. Of the 8 patients who developed K65R in the tenofovir arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and the last one at week 96. Among these patients, 5/8 patients subsequently gained full virologic control (<50 copies/mL) upon switching to new regimens that included a protease inhibitor in combination with nucleoside reverse transcriptase inhibitors through a median of 155 weeks of follow-up. One patient in the tenofovir arm developed K70E substitution in the virus. From both genotypic and phenotypic analyses there was no evidence for other pathways of resistance to tenofovir.

Figure 2 Percentage of patients with HIV RNA < 400 using Intent-to-treat analysis through Week 144: Study 903 (Missing=Failure, Switch=Failure)



Study 934: tenofovir disoproxil + Emtriva + efavirenz compared with Combivir® (lamivudine + zidovudine + Efavirenz)

Study 934 is a randomised, open-label, active controlled multicentre study comparing two different dosing regimens in 511 antiretroviral-naïve HIV-1 infected patients. Patients were randomised to receive either EMTRIVA + tenofovir disoproxil administered in combination with efavirenz or Combivir (lamivudine/zidovudine) administered in combination with efavirenz. For patients randomised to receive

EMTRIVA + tenofovir disoproxil the two drugs were administered individually for the first 96 weeks and then switched to TRUVADA (fixed dose combination of tenofovir disoproxil (as fumarate) 300 mg/emtricitabine 200 mg) during weeks 96 to 144, without regard to food.

For inclusion in the study, antiretroviral treatment naïve adult patients (≥ 18 years) with plasma HIV RNA greater than 10,000 copies/mL, must have an estimated glomerular filtration rate as measured by Cockcroft-Gault method of ≥ 50 mL/min, adequate haematologic function, hepatic transaminases and alanine aminotransferases ≤ 3 ULN, total bilirubin ≤ 1.5 mg/dL, serum amylase ≤ 1.5 ULN and serum phosphorus ≥ 2.2 mg/dL. Exclusion criteria included: a new AIDS defining condition diagnosed within 30 days (except on the basis of CD4 criteria), ongoing therapy with nephrotoxic drugs or agents that interacted with efavirenz, pregnancy/lactation, a history of clinically significant renal / bone disease or malignant disease other than Kaposi's sarcoma or basal-cell carcinoma, or a life expectancy of less than one year. If efavirenz-associated central nervous system toxicities occurred, nevirapine could be substituted for efavirenz. Patients who were not receiving their originally assigned treatment regimen after week 48 or 96 and during the 30-day extension study window were not eligible to continue to weeks 96 or 144 respectively.

Patients had a mean age of 38 years (range 18 to 80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4 cell count was 245 cells/mm^3 (range 2 to 1191) and median baseline plasma HIV-1 RNA was 5.01 log10 copies/mL (range 3.56 to 6.54). Patients were stratified by baseline CD4 count (< or ≥ 200 cells/mm^3); 41% had CD4 cell counts <200 cells/mm^3 and 51% of patients had baseline viral loads >100,000 copies/mL. Treatment outcomes at 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 15.

Table 15. Outcomes of Randomised Treatment at Weeks 48 and 144 (Study 934) in Treatment Naïve Patients

Outcome at Weeks 48 and 144	WEEK 48		WEEK 144	
	TENOFOVIR DISOPROXIL +EMTRIVA+ EFV (N=244)	Combivir + EFV (N=243)	TRUVADA[4] + EFV (N=227)	Combivir + EFV (N=229)
Responder[1]	84%	73%	71%	58%
Virologic failure[2]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death[3]	<1%	1%	1%	1%

1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL.
3. All deaths were unrelated to study drugs.
4. Patients received TENOFOVIR DISOPROXIL + EMTRIVA up to week 96 and switched to TRUVADA from week 96 to 144

In this study, tenofovir disoproxil + EMTRIVA in combination with efavirenz was statistically significantly superior to Combivir in combination with efavirenz with regards to the primary and secondary endpoints: achieving and maintaining HIV-1 RNA < 400 copies/mL through 48 and 144 weeks (Table 15). The difference in the proportions of responders between the tenofovir disoproxil + EMTRIVA group and the Combivir group was 11.4%, and the 95% CI was 4.3% to 18.6% (p=0.002) at week 48 and a difference of 12.9% (95% CI was 4.2% to 21.6%, p=0.004) at week 144.

Through 48 weeks of therapy, 80% and 70% of patients in the tenofovir disoproxil + EMTRIVA and the Combivir arms, respectively, achieved and maintained HIV-1 RNA <50 copies/mL. The difference in the proportions of responders between tenofovir disoproxil + EMTRIVA group and the Combivir group was 9.1%, and the 95% CI was 1.6% to 16.6% (p=0.021) at week 48. The proportion of patients responding at 144 weeks

of therapy was higher in the TRUVADA group (64%) compared with the Combivir group (56%); p=0.082, a difference of 8.1% and the 95% CI was -0.8% to 17.0%.

The mean increase from baseline in CD4 cell count was 190 cells/mm^3 and 312 cells/mm^3 for the tenofovir disoproxil + EMTRIVA + efavirenz arm, and 158 cells/mm^3 and 271 cells/mm^3 for the Combivir + efavirenz arm (p=0.002 and p = 0.088) at weeks 48 and 144 respectively.

Resistance analysis was performed on HIV isolates from all patients with > 400 copies/mL of HIV-1 RNA at week 144 while on study drug or after treatment switch. Genotypic resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed in both treatment groups. Resistance to efavirenz occurred in 68% (13/19) analysed patients in the TRUVADA group and in 72% (21/29) analysed patients in the Combivir group. The M184V mutation, associated with resistance to emtricitabine and lamivudine, developed significantly less in the analysed patients in the TRUVADA group 11% (2/19) compared with the analysed patients in the Combivir group, 34% (10/29). Two patients in the Combivir group developed thymidine analog mutations, specifically D67N or K70R mutations in the reverse transcriptase gene. No patient in either treatment group developed the K65R or K70E mutation, which is associated with reduced susceptibility to tenofovir.

Genotypic Analyses of tenofovir in Patients with Previous Antiretroviral Therapy (Study 902 and 907)

The virologic response to tenofovir therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment experienced patients participating in trials 902 and 907. In both of these studies, 94% of the participants evaluated had baseline HIV isolates expressing at least one NRTI mutation. These included resistance mutations associated with zidovudine (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N), the lamivudine/abacavir-associated mutation (M184V), and others. In addition the majority of participants evaluated had mutations associated with either PI or NNRTI use. Virologic responses for patients in the genotype substudy were similar to the overall results in studies 902 and 907.

Several exploratory analyses were conducted to evaluate the effect of specific mutations and mutational patterns on virologic outcome. Descriptions of numerical differences in HIV RNA response are displayed in Table 16. Because of the large number of potential comparisons, statistical testing was not conducted.

Varying degrees of cross-resistance to tenofovir from pre-existing zidovudine-associated mutations were observed and appeared to depend on the number and type of mutations. Tenofovir disoproxil-treated patients whose HIV expressed 3 or more zidovudine-associated mutations that included either the M41L or L210W reverse transcriptase mutation showed reduced responses to tenofovir therapy; however, these responses were still improved compared with placebo. The presence of the D67N, K70R, T215Y/F or K219Q/E/N mutation did not appear to affect responses to tenofovir therapy. The HIV RNA responses by number and type of baseline zidovudine-associated mutations are shown in Table 16.

Table 16. HIV RNA Response at Week 24 by Number of Baseline Zidovudine-Associated Mutations in Studies 902 and 907 (Intent-To-Treat) [1]

Number of baseline zidovudine-associated mutations[2]	**Change in HIV RNA[3] (N)**	
	TENOFOVIR DISOPROXIL	**Placebo**
None	-0.80 (68)	-0.11 (29)
Any	-0.50 (154)	0 (81)
1 – 2	-0.66 (55)	-0.04 (33)
≥ 3 including M41L or L210W	-0.21 (57)	+0.01 (29)
≥ 3 without M41L or L210W	-0.67 (42)	+0.07 (19)

1. Genotypic testing performed by Virco Laboratories and Visible Genetics TruGeneTM technology
2. M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N in RT
3. Average HIV RNA change from baseline through week 24 (DAVG24) in log10 copies/mL

In the protocol defined analyses, virologic response to tenofovir disoproxil was not reduced in patients with HIV that expressed the lamivudine/ abacavir-associated M184V mutation. In the absence of zidovudine-associated mutations, patients with the M184V mutation receiving tenofovir disoproxil showed a –0.84 log10 copies/mL decrease in their HIV RNA relative to placebo. In the presence of zidovudine-associated mutations, the M184V mutation did not affect the mean HIV RNA responses to tenofovir treatment. HIV-1 RNA responses among these patients were durable through week 48.

There was limited data on patients expressing some primary nucleoside reverse transcriptase inhibitor mutations and multi-drug resistant mutations at baseline. However, patients expressing mutations at K65R (N=6), or L74V without zidovudine-associated mutations (N=6) appeared to have reduced virologic responses to tenofovir.

The presence of at least one HIV protease inhibitor or non-nucleoside reverse transcriptase inhibitor mutation at baseline did not appear to affect the virologic response to tenofovir. Cross resistance between tenofovir and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

Phenotypic Analyses of tenofovir in Patients with Previous Antiretroviral Therapy (Study 902 and 907)

The virologic response to tenofovir therapy has been evaluated with respect to baseline phenotype (N=100) in treatment experienced patients participating in trials 902 and 907. Phenotypic analysis of baseline HIV from patients in Studies 902 and 907 demonstrated a correlation between baseline susceptibility to tenofovir and response to tenofovir therapy. Table 17 summarises the HIV RNA response by baseline tenofovir susceptibility.

Table 17. HIV RNA Response at Week 24 by Baseline TENOFOVIR Susceptibility in Studies 902 and 907 (Intent-To-Treat) [1]

Baseline tenofovir Susceptibility[2]	Change in HIV RNA[3] (N)
≤1	-0.74 (35)
>1 and ≤3	-0.56 (49)
>3 and ≤4	-0.3 (7)
≤4	-0.61 (91)
> 4	-0.12 (9)

1. Tenofovir susceptibility was determined by recombinant phenotypic AntivirogramTM assay (Virco)
2. Fold change in susceptibility from wild-type
3. Average HIV RNA change from baseline through week 24 (DAVG24) in log10 copies/mL

Clinical efficacy in chronic hepatitis B:

The demonstration of benefit of tenofovir is based on histological, virological, biochemical, and serological responses in adults with HBeAg positive and HBeAg negative chronic hepatitis B with compensated and decompensated liver function; clinical evidence of prior treatment failure; and patients co-infected with HIV-1 and HBV. In these clinical studies patients had active viral replication at baseline. Tenofovir has demonstrated anti-HBV activity in patients with HBV containing lamivudine- or adefovir-resistance-associated mutations.

Study 0102 and 0103: tenofovir disoproxil compared with HEPSERA (adefovir dipivoxil)

Results through 48 weeks from 2 Phase 3 randomised, double-blind studies comparing tenofovir disoproxil to HEPSERA in patients with compensated liver disease are presented in Table 18 below. Study GS-US-174-0103 (0103) was conducted in 266 (randomised and treated) HBeAg positive patients while study GS-US-174-0102 (0102) was conducted in 375 (randomised and treated) patients who were negative for HBeAg and positive for HBeAb.

In both of these studies tenofovir disoproxil was statistically significantly superior to HEPSERA 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 score).

Treatment with tenofovir disoproxil (as fumarate) 300 mg was also associated with significantly greater proportions of patients with HBV DNA < 400 copies/ml, when compared to HEPSERA 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 score) at Week 48 (see Table 18 below).

In study 0103 a significantly greater proportion of patients in the tenofovir group than in the HEPSERA group had normalised ALT and achieved HBsAg loss at Week 48 (see Table 18 below).

Table 18. Clinical Outcomes of Randomised Treatment (Study 0102 and 0103) at Week 48

	Study 0102 (HBeAg Negative)		**Study 0103 (HBeAg Positive)**	
Parameter	**TENOFOVIR DISOPROXIL n= 250**	**HEPSERA n= 125**	**TENOFOVIR DISOPROXIL n= 176**	**HEPSERA n= 90**
Complete Response (%)[1]	71*	49	67*	12
Histology Histological Response (%)[2]	72	69	74	68
HBV DNA (%) < 400 copies/ml (<69 IU/ml)	93*	63	76*	13
ALT (%) Normalised ALT[3]	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 vs HEPSERA <0.05.

1. 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 score.
2. Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.
3. The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.

Tenofovir disoproxil was associated with statistically 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 HEPSERA (study 0102; 91%, and 56% and study 0103; 69% and 9%) respectively.

Response to treatment with tenofovir disoproxil 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 0102 and 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.

Treatment Beyond 48 weeks (Studies 0102 and 0103):

In studies 0102 (n=347) and 0103 (n=238), after receiving double-blind treatment for 48 weeks (either tenofovir disoproxil or HEPSERA), patients rolled over with no treatment interruption, to open-label tenofovir disoproxil.

In study 0102, 266 of 347 patients (77%) continued through week 384, while in study 0103, 146 of 238 (61%) continued through week 384. At weeks 96, 144, 192, 240, 288 and 384 viral suppression, biochemical and serological responses were maintained with continued tenofovir treatment (see Table 19 and 20 below).

Table 19. Virological, Biochemical and Serological Response at Weeks 96, 144, 192, 240, 288 and 384 (Study 0102)

Outcomes[a]	Study 0102 (HBeAg Negative)											
	TENOFOVIR DISOPROXIL (n= 250)						HEPSERA Rollover to Tenofovir disoproxil (n= 125)					
Week	**96[b]**	**144[e]**	**192[h]**	**240[j]**	**288[k]**	**384[n]**	**96[c]**	**144[f]**	**192[h]**	**240[j]**	**288[l]**	**384[o]**
HBV DNA (%) < 400 copies/mL (<69 IU/mL)	90	87	84	83	80	74	89	88	87	84	84	76
HBV DNA (%) < 169 copies/ml (<29 IU/mL)	89	86	83	82	80	74	89	88	87	84	84	76
ALT (%) Normalised ALT[d]	72	73	67	70	68	64	68	70	77	76	74	69
Serology (%) HBsAg Loss[p]	0	0	0	0	0	1	0	0	0	0	1	1
Seroconversion [q]	0	0	0	0	0	0	0	0	0	0[m]	1	1

a) Based upon Long-Term Evaluation Algorithm (LTE Analysis) – Patients who discontinued the study at any time prior to week 288 due to a protocol defined endpoint, as well as those completing week 288, are included in the denominator,
b) 48 weeks double-blind tenofovir disoproxil followed by up to 48 weeks open-label,
c) 48 weeks double-blind HEPSERA followed by up to 48 weeks open-label tenofovir disoproxil,
d) The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline,
e) 48 weeks double-blind tenofovir disoproxil followed by 96 weeks open-label,
f) 48 weeks double-blind HEPSERA followed by 96 weeks open-label tenofovir disoproxil,
g) 48 weeks double-blind tenofovir disoproxil followed by 144 weeks open-label,
h) 48 weeks double-blind HEPSERA followed by 144 weeks open-label tenofovir disoproxil,
i) 48 weeks double-blind tenofovir disoproxil followed by 192 weeks open-label.
j) 48 weeks double-blind HEPSERA followed by 192 weeks open-label tenofovir disoproxil.
k) 48 weeks double-blind tenofovir disoproxil followed by 240 weeks open-label (n=192/235 (82%))
l) 48 weeks double-blind HEPSERA followed by 240 weeks open-label tenofovir disoproxil (n= 101/112 (91%))
m) 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.
n) 48 weeks double-blind tenofovir followed by 336 weeks open labelled tenofovir disoproxil
o) 48 weeks double-blind HEPSERA followed by 336 weeks open labelled tenofovir disoproxil
p) Figures presented are cumulative percentages based upon a Kaplan Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir disoproxil (KM-TDF)
q) Figures presented are cumulative percentages based upon a Kaplan Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir disoproxil (KM-TDF)

n/a = Not Applicable Patients with HBV DNA ≥400 copies/mL at week 72 or later were eligible to receive intensification therapy with open-label TRUVADA (tenofovir disoproxil/emtricitabine) and results from these patients are not included as responders in this table (intensification therapy = failure). Results from the Tenofovir 384 week treatment groups including these patients were 81% for HBV DNA < 400 copies/mL and 70% for normalised ALT, for study 0102

Table 20. Virological, Biochemical and Serological Response at Weeks 96, 144, 192, 240, 288 and 384 (Study 0103)

Outcomes[a]	Study 0103 (HBeAg Positive)	
	Tenofovir disoproxil (n= 176)	**HEPSERA Rollover to tenofovir disoproxil (n= 90)**

Week	96[b]	144[e]	192[h]	240[j]	288[l]	384[o]	96[c]	144[f]	192[i]	240[k]	288[m]	384[p]
HBV DNA (%) < 400 copies/mL (<69 IU/mL)	76	72	68	64	61	56	74	71	72	66	65	61
HBV DNA (%) < 169 copies/ml (<29 IU/mL)	73	70	68	63	61	56	74	70	70	66	65	61
ALT (%) Normalised ALT [d]	60	55	56	46	47	47	65	61	59	56	57	56
Serology (%) HBsAg Loss	26	29	34	38	37	30	24	33	36	38	40	35
Seroconversion	23	23	25	30	25	20	20	26	30	31	31	24
HbsAg Loss	5	8[g]	11[g]	11[n]	12[n]	15[n]	6	8[g]	8[g]	10[n]	11[n]	13[n]
Seroconversion	4	6[g]	8[g]	8[n]	8[n]	12[n]	5	7[g]	7[g]	10[n]	10[n]	11[n]

a) Based upon Long-Term Evaluation Algorithm (LTE Analysis) – Patients who discontinued the study at any time prior to week 288 due to a protocol defined endpoint, as well as those completing week 288, are included in the denominator,
b) 48 weeks double-blind tenofovir disoproxil followed by up to 48 weeks open-label,
c) 48 weeks double-blind HEPSERA followed by up to 48 weeks open-label tenofovir disoproxil,
d) The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline,
e) 48 weeks double-blind tenofovir disoproxil followed by 96 weeks open-label,
f) 48 weeks double-blind HEPSERA followed by 96 weeks open-label tenofovir
g) Figures presented are cumulative percentages based upon a Kaplan Meier analysis (KM-ITT),
h) 48 weeks double-blind tenofovir disoproxil followed by 144 weeks open-label,
i) 48 weeks double-blind HEPSERA followed by 144 weeks open-label tenofovir disoproxil,
j) 48 weeks double-blind tenofovir disoproxil followed by 192 weeks open-label.
k) 48 weeks double-blind HEPSERA followed by 192 weeks open-label tenofovir disoproxil.
l) 48 weeks double-blind tenofovir disoproxil followed by 240 weeks open-label (n=106/154 (69%))
m) 48 weeks double-blind HEPSERA followed by 240 weeks open-label tenofovir disoproxil (n=67/84 (80%))
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 (KM-TDF).
o) 48 weeks double-blind tenofovir disoproxil followed by 336 weeks open-label tenofovir disoproxil
p) 48 weeks double-blind HEPSERA followed by 336 weeks open-label tenofovir disoproxil

n/a = Not Applicable. Patients with HBV DNA ≥400 copies/mL at week 72 or later were eligible to receive intensification therapy with open-label TRUVADA (tenofovir disoproxil/emtricitabine) and results from these patients are not included as responders in this table (intensification therapy = failure). Results from the tenofovir 384 week treatment groups including these patients were 69% for HBV DNA < 400 copies/mL and 52% for normalised ALT and 38%/27% for HBeAg loss/seroconversion.

Paired baseline and week 240 liver biopsy data were available for 331/489 patients who remained in studies 0102 and 0103 (see Table 21 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 reversal of cirrhosis by week 240 with a reduction in Ishak fibrosis score of at least 2 points except for one patient with an initial Ishak score of five.

Table 21: Histological response (%) in compensated HBeAg negative and HBeAg positive subjects at week 240 compared to baseline

	Study 0102 (HBeAg negative)		Study 0103 (HBeAg positive)	
	tenofovir disoproxil n = 250[c]	HEPSERA Rollover to tenofovir disoproxil n = 125[d]	tenofovir disoproxil n = 176[c]	HEPSERA Rollover to tenofovir disoproxil n = 90[d]
Histological response [a,b] (%)	88 [130/148]	85 [63/74]	90 [63/70]	92 [36/39]

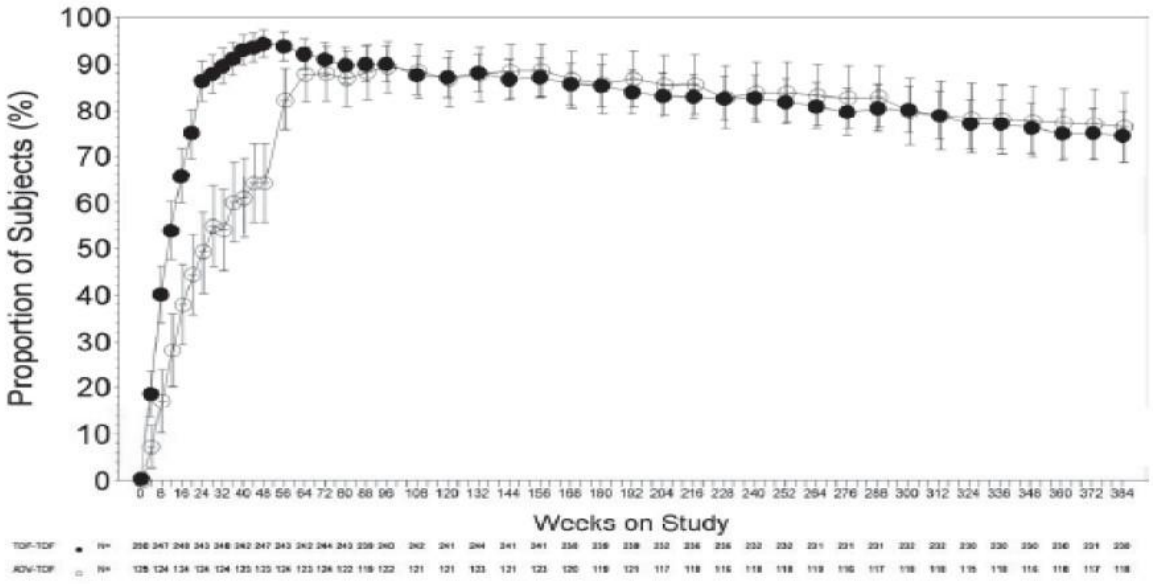
a) The population used for analysis of histology included only patients with available liver biopsy data (Missing = Excluded) by week 240. Response after addition of emtricitabine is excluded (total of 17 subjects across both studies).
b) Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.
c) 48 weeks double-blind tenofovir disoproxil followed by up to 192 weeks open-label.
d) 48 weeks double-blind HEPSERA followed by up to 192 weeks open-label tenofovir disoproxil.

When the data were evaluated including only patients that completed 384 weeks of therapy (observed (missing data is excluded) and data after the addition of emtricitabine included; on therapy analysis), in the group of patients who received 48 weeks of double-blind treatment with tenofovir disoproxil followed by open-label treatment with tenofovir disoproxil; 99% (173 of 174) and 100% (88 of 88) of patients had HBV DNA < 400 copies/mL and 88% (141 of 160) and 81% (70 of 86) of patients had ALT normalisation at week 384, in studies 0102 and 0103 respectively. In study 0103, HBeAg loss was reported for 44% (31 of 70) of patients and 28% (19 of 68) of patients experienced HBeAg seroconversion. 14% of patients experienced HBsAg loss and 12% of patients experienced HBsAg seroconversion by week 384. In Study 102, HBsAg loss and seroconversion were 1% in both treatment group.

Similarly (using the on-therapy analysis), in the group of patients who received 48 weeks of double-blind treatment with HEPSERA followed by open-label treatment with tenofovir disoproxil; 100% (90/90) and 95% (55/58) of patients had HBV DNA < 400 copies/mL and 88% (74 of 84) and 88% (50/57) of patients had ALT normalisation, at week 384, in studies 0102 and 0103 respectively. In study 0103, HBeAg loss was reported for 50% (24/48) of patients and 36% (17/47) of patients experienced HBeAg seroconversion. HBsAg loss was experienced in 13% and 11% of patients experienced HBsAg seroconversion, while on tenofovir disoproxil.

The proportion of patients in studies 0102 and 0103 with HBV DNA < 400 copies/mL are shown in Figures 3 and 4.

Figure 3 Proportion (95% CI) of Patients with HBV DNA <400 copies/mL by Visit Full Analysis Set (Study 0102)

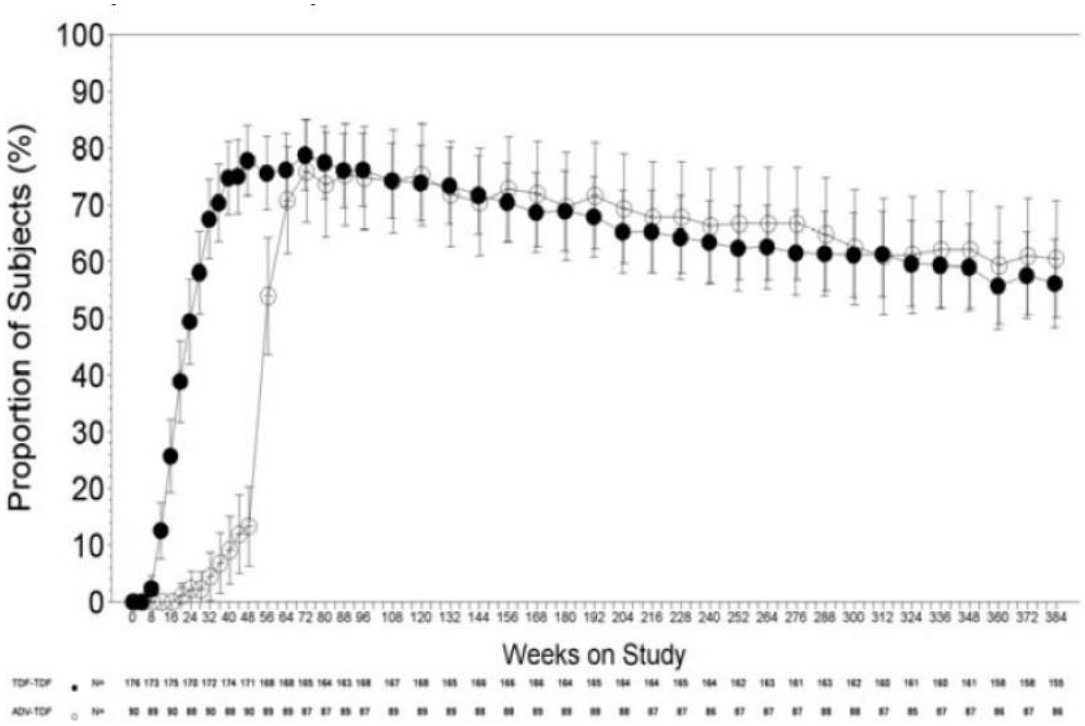


Randomised and treated patients, LTE Algorithm (Long-Term Evaluation/Addition of FTC=Failure (LTE-TDF); 384 week data is also reported in Table 19.

TDF•: 48 weeks double-blind tenofovir disoproxil followed by up to 336 weeks open-label.

ADV°: (Adefovir dipivoxil) 48 weeks double-blind HEPSERA followed by up to 336 weeks open-label tenofovir disoproxil.

Figure 4 Proportion of Patients (95% CI) with HBV DNA <400 copies/mL by Visit Full Analysis Set (Study 0103)



Randomised and treated patients, LTE Algorithm (Long-Term Evaluation/Addition of FTC=Failure (LTE-TDF); 384 week data is also reported in Table 20.

TDF•: 48 weeks double-blind Tenofovir disoproxil followed by up to 336 weeks open-label.

ADVº: (Adefovir dipivoxil): 48 weeks double-blind HEPSERA followed by up to 336 weeks open-label tenofovir disoproxil.

Nucleos(t)ide Experienced Patients

Experience with Patients with Lamivudine Resistance (Study GS-US-174-0121)

The efficacy and safety of tenofovir disoproxil (as fumarate) or 200 mg emtricitabine plus 300 mg tenofovir disoproxil (as fumarate) were evaluated in a randomised, double-blind study, in HBeAg-positive and HBeAg negative patients with viremia (HBV DNA ≥ 1,000 IU/mL) and genotypic evidence of lamivudine resistance (rtM204I/V +/- rtL180M). One hundred and forty-one adult subjects were randomised to the tenofovir treatment arm. The mean age of subjects randomised to tenofovir was 47 years (range 18-73), 74% were male, 59% were Caucasian, and 37% were Asian. At baseline, 54% of subjects were HBeAg-negative, 46% were HBeAg-positive, and 56% had abnormal ALT. Subjects had a mean HBV DNA of 6.4 log10 copies/mL and mean serum ALT of 71 U/L at baseline.

After 96 weeks of treatment, 126 of 141 subjects (89%) randomised to tenofovir disoproxil had HBV DNA < 400 copies/mL, and 49 of 79 subjects (62%) had ALT normalisation. Among the HBeAg-positive subjects randomised to tenofovir disoproxil, 10 of 65 subjects (15%) experienced HBeAg loss, and 7 of 65 subjects (11%) experienced anti-Hbe seroconversion through Week 96.

Experience with Patients Co-infected with HIV and HBV (Study ACTG 5127)

In a randomised, 48 week double-blind, non-inferiority trial, tenofovir disoproxil (as fumarate) (TDF) 300 mg daily was compared with HEPSERA (ADV) 10 mg daily in the treatment of chronic hepatitis B patients who were co-infected with HIV and were stable on antiretroviral therapy. Mean baseline serum HBV DNA were 9.45 log10 copies/ml and 8.85 log10 copies/ml in subjects randomised to TDF (n=27) and ADV (n=25), respectively. In subjects for whom there was week 48 data (n=35), the mean change from baseline in serum

HBV DNA was -5.74 log10 copies/ml for the TDF group (n=18) and -4.03 log10 copies/ml for the ADV group (n=17), respectively. A total of 61 % of subjects (36% in the TDF group and 25% in the ADV group) had normalised serum ALT at week 48, but the differences were not statistically significant. The study showed that over 48 weeks, treatment with either ADV or TDF resulted in clinically important suppression of serum HBV DNA and TDF was not inferior to ADV in HBV viral suppression.

Experience in Patients who had Incomplete Viral Response to HEPSERA (Study 0106)

The efficacy and safety of tenofovir disoproxil (as fumarate) 300 mg or TRUVADA (tenofovir DF/emtricitabine) is being evaluated in a randomised, double-blind study (Study GS-US-174-0106, 0106), in HBeAg positive and HBeAg negative patients who had persistent viraemia (HBV DNA ≥ 1000 copies/ml) while receiving HEPSERA 10 mg for more than 24 weeks. Overall at Week 48, treatment with tenofovir disoproxil resulted in 66% (35/53) of patients with HBV DNA < 400 copies/ml and 64% (34/53) of patients with undetectable HBV DNA (below 169 copies/ml the limit of quantification of the Roche Cobas TaqMan HBV assay); patients that discontinued prior to 48 weeks, including those who received intensification therapy (TRUVADA (tenofovir disoproxil/emtricitabine) were excluded. In addition, at Week 48, the percentage of patients who had ALT normalisation was 33% (9/27).

In study 0106, patients were also analysed based upon lamivudine- or adefovir-resistant HBV results at baseline; patients that discontinued prior to 48 weeks were considered as failures. Table 22 below summarises Week 48 results of patients treated with tenofovir disoproxil.

Table 22. Summary of Clinical Efficacy at Week 48 (Study 0106): RAT Analysis Set

	TENOFOVIR DISOPROXIL (n=53)
HBV DNA < 400 copies/mL, n(%)[1]	**43 (81%)**
Lamivudine-resistant patients, n/N (%)[1]	6/7 (86%)
Adefovir-resistant patients, n/N (%)[1]	7/8 (88%)
HBV DNA < 169 copies/mL[1]	**40 (76%)**
Lamivudine-resistant patients, n/N (%)[1]	5/7 (72%)
Adefovir-resistant patients, n/N (%)[1]	7/8 (88%)
Normalised ALT[1, 2]	**11/27 (41%)**
Lamivudine-resistant patients, n/N (%)[1]	3/4 (75%)
Adefovir-resistant patients, n/N (%)[1]	3/5 (60%)
HBeAg Loss[1, 3]	**3/38 (8%)**
HBeAg Seroconversion[1, 3]	**2/38 (5%)**
HBsAg Loss[1, 3]	**1/53 (2%)**
HBsAg Seroconversion[1, 3]	**1/53 (2%)**

a) Patients who prematurely discontinued the study prior to week 48 were considered failures at all time points following the time of discontinuation.
b) Normalised ALT defined as ALT at or below the ULN, for subjects with above the ULN at baseline.
c) HBeAg/HBsAg loss defined as HBeAg/HBsAg result for those subjects with positive HBeAg/HBsAg at baseline. Seroconversion defined as HBeAg/HBsAg loss and positive anti-HBe/anti-HBs result.

At week 48, no patient with lamivudine- or adefovir-resistant mutations at baseline, had HBeAg/HBsAg loss and/or seroconversion.

Experience in Patients with Decompensated Liver Disease at 48 weeks (Study 0108)

Study GS-US-174-0108 (0108) is a randomised, double-blind, active controlled study evaluating the safety and efficacy of tenofovir disoproxil (n=45) for 48 weeks in patients with decompensated liver disease. In the

tenofovir treatment arm, patients had a mean Child-Pugh-Turcotte (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 and 9 of 45 patients (20%) had lamivudine and/or adefovir resistance substitutions at baseline. The coprimary safety endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine ≥ 0.5 mg/dL or confirmed decrease in serum phosphorus of < 2 mg/dL.

In the tenofovir treatment arm, 3 of 45 patients (7%) discontinued treatment due to an adverse event; 4 of 45 (9%) experienced a confirmed increase in serum creatinine of ≥ 0.5 mg/dL or confirmed decrease in serum phosphorus of < 2 mg/mL through week 48; these results were similar to those in the non-tenofovir containing treatment arm. HBV DNA < 400 copies/mL and normal ALT were observed in 31 of 44 patients (70%) and 25 of 44 patients (57%), respectively, in the tenofovir treatment arm. The mean change from baseline in CPT score was -0.8; the mean absolute CPT score was 6 at week 48.

After 168 weeks, 16% (7 of 45) of the tenofovir group, 4% (2 of 45) of the emtricitabine plus tenofovir group, and 14% (3 of 22) of the entecavir group experienced tolerability failure. Thirteen percent (6 of 45) of the tenofovir group, 13% (6 of 45) of the emtricitabine plus tenofovir group, and 9% (2 of 22) of the entecavir group had a confirmed increase in serum creatinine ≥ 0.5 mg/dl or confirmed serum phosphate of < 2 mg/dl.

Experience in Paediatric Patients 12 Years of Age and Older (Study 0115)

In Study GS-US-174-0115 (0115), 106 HBeAg negative and positive patients aged 12 to < 18 years with chronic HBV infection [HBV DNA $\geq 10^5$ 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 (n=52) or placebo (n=54) for 72 weeks. At Week 72, 88% (46/52) of patients in the tenofovir 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 group had normalised ALT at Week 72 compared to 31% (13/42) in the placebo group. Response to treatment with tenofovir disoproxil was comparable in nucleos(t)ide-naïve patients (n=20) and nucleos(t)ide-experienced (n=32) patients. Ninety-five percent of nucleos(t)ide-naïve patients and 84% nucleos(t)ide-experienced patients achieved HBV DNA < 400 copies/mL at Week 72. At week 72, 96% (27/28) of immune-active patients (HBV DNA $\geq 10^5$ copies/ml, serum ALT > 1.5 x ULN) in the tenofovir 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 group had normal ALT at week 72 compared to 34% (11/32) in the placebo group.

Clinical Resistance

Of 279 HBeAg negative and HBeAg positive patients who received treatment with tenofovir disoproxil for up to 384 weeks in studies 0102 and 0103, genotypic analysis was performed on HBV isolates for all patients with HBV DNA > 400 copies/mL (n=2). No amino acid substitutions occurred in these subjects' isolates which were associated with tenofovir resistance.

In studies 0102 and 0103, 152 patients treated with HEPSERA for 48 weeks, rolled over to treatment with tenofovir disoproxil for up to 366 weeks; two patients with HBV DNA remaining > 400 copies/mL was evaluated for resistance. No amino acid substitutions occurred in these subjects' isolates which were associated with tenofovir resistance.

Among the 53 treatment-experienced patients in study 0106 treated with tenofovir disoproxil, 17 had HBV DNA > 400 copies/mL following up to 48 weeks of treatment with tenofovir disoproxil. Among these patients, no amino acid substitutions were observed in association with tenofovir resistance.

In study 0108, 45 patients (including 9 patients with lamivudine and/or adefovir resistance substitutions at baseline) received tenofovir disoproxil for up to 168 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 8 of 9 patients with HBV DNA > 400 copies/mL. No amino acid substitutions associated with tenofovir resistance were identified in these isolates.

In studies 0102, 0103 and 0106, 12 patients randomised to tenofovir disoproxil had HBV containing lamivudine-resistance associated substitutions at baseline. Following up to 48 weeks (0106; n=7) or 240 weeks

(0102 and 0103; n =4) of treatment with tenofovir disoproxil, two patients in study 0106 had HBV DNA > 400 copies/mL; no amino acid substitutions were observed in association with tenofovir resistance.

In studies 0102, 0103 and 0106, 13 patients treated with tenofovir disoproxil had adefovir-resistance associated substitutions at baseline. Following up to 48 weeks (0106; n=8) or 240 weeks (0102 and 0103; n=5) of treatment with tenofovir disoproxil, one patient in study 0103 and two patients in study 0106 had HBV DNA > 400 copies/mL; no amino acid substitutions were observed in association with tenofovir resistance.

In a paediatric study (GS-US-174-0115), HBV isolates from 5 patients who had plasma HBV DNA > 400 copies/mL were evaluated for tenofovir resistance-associated substitutions. No amino acid substitutions associated with resistance to tenofovir were identified in these isolates by Week 72.

In study 0121, 141 patients with lamivudine resistance substitutions at baseline received tenofovir disoproxil 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. No amino acid substitutions associated with resistance to tenofovir were identified in these isolates.

Cross Resistance

Cross-resistance has been observed among HBV reverse transcriptase inhibitors. In cell based assays, HBV strains expressing the rtV173L, rtL180M and rtM204I/V mutations associated with resistance to lamivudine, telbivudine and reduced susceptibility to entecavir 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 EC_{50} values 1.5-fold that of wild type virus.

5.2 PHARMACOKINETIC PROPERTIES

TENOFOVIR DISOPROXIL VIATRIS contains 300mg tenofovir disoproxil maleate salt compared to the innovator product which contained 300mg tenofovir disoproxil fumerate salt. All clinical data in this product information (including Pharmacokinetic, Pharmacodynamic, and Clinical Trial data) are based on tenofovir disoproxil fumerate.

Pharmacokinetic bioequivalence has been established between the two salt forms based on 'tenofovir' levels in blood. The results (Test/Reference) were as follows:

Tenofovir	Geometric Mean Ratio (Test/Reference)	90% Confidence Interval
C_{max}	104.3	97.88 – 111.08
AUC_t	101.5	98.50 – 104.54
AUC_∞	101.8	99.09 – 104.51

Tenofovir disoproxil maleate is a water soluble ester prodrug of the active ingredient tenofovir. Tenofovir is converted intracellularly to tenofovir monophosphate and tenofovir diphosphate. The pharmacokinetics of Tenofovir disoproxil (as fumarate) have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

Following oral administration, tenofovir disoproxil maleate is rapidly absorbed and converted to tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil (as fumarate) in fasted patients was approximately 25%. Following oral administration of a single dose of tenofovir disoproxil (as fumarate) 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (Cmax) are achieved in 1.0 ± 0.4 hrs. Cmax and AUC values are 296 ± 90 ng/mL and 2287 ± 685 ng•h/mL, respectively.

Effects of Food on Oral Absorption

Administration of tenofovir disoproxil (as fumarate) following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in Cmax of approximately 14%. Food delays the time to tenofovir Cmax by approximately 1 hour. Cmax and AUC of tenofovir are 326 ± 119 ng/mL and 3324 ± 1370 ng•h/mL following multiple doses of tenofovir disoproxil (as fumarate) 300 mg once daily in the fed state, when meal content was not controlled.

Distribution

After oral administration of tenofovir disoproxil (as 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 human plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 μg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism

In vitro studies have determined that neither tenofovir disoproxil (as fumarate) nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (~ 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 (as fumarate) at a concentration of 100 μM 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. Based on these data, it is unlikely that clinically significant drug-drug interactions involving tenofovir disoproxil and medicinal products metabolised by CYP450 would occur.

Excretion

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Linearity/non-linearity

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

Special Populations

Gender

Pharmacokinetics of tenofovir in patients are similar with regard to gender.

Paediatric Patients 12 Years of Age and Older

Steady-state pharmacokinetics of tenofovir were evaluated in eight HIV-1 infected paediatric patients (12 to <18 years). Mean (± SD) Cmax and AUCtau are 0.38 ± 0.13 μg/mL and 3.39 ± 1.22 μg•hr/mL, respectively. Tenofovir exposure achieved in paediatric patients aged 12 years of age and older receiving oral daily doses of tenofovir disoproxil (as fumarate) 300 mg were similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil (as fumarate) 300 mg.

Tenofovir exposure in HBV infected paediatric patients (12 to <18 years of age) receiving oral daily dose of tenofovir disoproxil (as fumarate) 300 mg tablet was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil (as fumarate) 300 mg.

Pharmacokinetic studies have not been performed with in paediatric subjects < 12 years of age.

Elderly Patients

Pharmacokinetic studies have not been performed in the elderly (> 65 years).

Ethnicity

Pharmacokinetics have not been specifically studied in different ethnic groups.

Renal Impairment

The pharmacokinetics of tenofovir are altered in subjects with renal impairment (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In non-HIV and non-HBV infected subjects with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, Cmax, and $AUC_{0-\infty}$ of tenofovir were increased (Table 23). It is required that the dosing interval for tenofovir be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Table 23. Pharmacokinetic Parameters (Mean ± SD) of Tenofovir disoproxil (as fumarate) * in Patients with varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min) [1]	**>80 (N=3)**	**50-80 (N=10)**	**30-49 (N=8)**	**12-29 (N=11)**
C_{max} (ng/mL)	335.5 ± 31.8	330.4 ± 61.0	372.1 ± 156.1	601.6 ± 185.3
$AUC_{0-\infty}$ (ng•hr/mL)	2184.5 ± 257.4	3063.8 ± 927.0	6008.5 ± 2504.7	15984.7 ± 7223.0
CL/F (mL/min)	1043.7 ± 15.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL_{renal} (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

*300 mg, single dose of tenofovir disoproxil (as fumarate)
[1]Creatinine clearance calculated using the Cockcroft Gault equation

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil (as fumarate), a four-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil (as fumarate) have been studied in non-HIV and non-HBV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in tenofovir dosing is required in patients with hepatic impairment.

Pharmacokinetic/pharmacodynamics relationship

Tenofovir disoproxil (as fumarate) has demonstrated a dose related significant and sustained anti-HIV effect at doses ranging from 75 mg to 300 mg.

Intracellular pharmacokinetics

In non-proliferating human peripheral blood mononuclear cells (PBMCs) *in vitro*, 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 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

In a long-term carcinogenicity study conducted in mice with tenofovir disoproxil (as fumarate) there was a low incidence of duodenal tumours with the highest dose of 600 mg/kg/day. These were associated with a

high incidence of duodenal mucosal hyperplasia, which was also observed with a dose of 300 mg/kg/day. These findings may be related to high local drug concentrations in the gastro-intestinal tract, likely to result in much higher exposure margins than that based on the AUC. At therapeutic doses the risk of these duodenal effects occurring in humans is likely to be low. The systemic drug exposure (AUC) with the 600 mg/kg/day dose was approximately 15 times the human exposure at the therapeutic dose of 300 mg/day. No tumourigenic response was observed in rats treated with doses of up to 300 mg/kg/day (5 times the human systemic exposure at the therapeutic dose based on AUC).

Tenofovir disoproxil was mutagenic in an *in vitro* mouse L5178Y lymphoma cell assay (tk locus) and in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes, but it was negative in *in vitro* bacterial assays for gene mutation and an *in vivo* mouse micronucleus test for chromosomal damage. Tenofovir base was not active in *in vitro* bacterial assays for gene mutation, and an equivocal response was seen in the *in vitro* mouse L5178Y lymphoma assay at a high concentration.

Animal Toxicology

Tenofovir and tenofovir disoproxil administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) between 6 and 12 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and /or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2-20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Fertility, pregnancy and lactation

Male and female rat fertility and mating performance or early embryonic development were unaffected by an oral tenofovir disoproxil (as fumarate) dose (600 mg/kg/day) that achieved systemic drug exposures that were in excess of the value in humans receiving the therapeutic dose (5-fold based on plasma AUC). There was, however, an alteration of the oestrous cycle in female rats.

Reproductive toxicity studies performed in rats and rabbits did not reveal any evidence of harm to the foetus due to tenofovir at respective exposures (AUC) of 4-13 and 66- fold the human exposure. Subcutaneous treatment of pregnant rhesus monkeys with a dose of 30 mg/kg/day of the tenofovir base during the last half of pregnancy resulted in reduced foetal serum phosphorus concentrations.

In animal studies tenofovir was excreted in milk after oral administration of tenofovir disoproxil (rats) and after subcutaneous administration of tenofovir base (non-human primates).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

TENOFOVIR DISOPROXIL VIATRIS tablet contains the following ingredients as excipients: Core: microcrystalline cellulose, lactose monohydrate, hyprolose, colloidal anhydrous silica, magnesium stearate Coating: OPADRY II complete film coating system 32K505018 BLUE (ARTG PI No: 109808).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

TENOFOVIR DISOPROXIL VIATRIS 300 mg tablets are marketed in high density polyethylene (HDPE) bottle with a child resistant closure in packs of 30.

Australian Register of Therapeutic Goods (ARTG)

AUST R 261093 – TENOFOVIR DISOPROXIL VIATRIS tenofovir disoproxil maleate 300 mg film coated tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

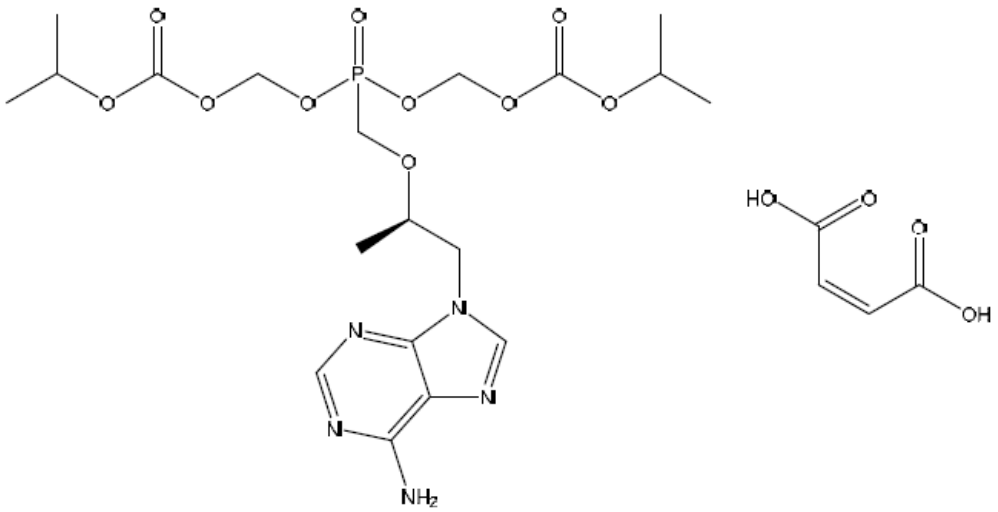
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name: Tenofovir disoproxil maleate is 9-[(R)-2 [[bis[[(isopropoxycarbonyl)oxy]methoxy]-phosphinyl]-methoxy]propyl]adenine maleate (1:1)

Structural formula



Molecular formula: $C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$ Molecular weight : 635.51

CAS Number

CAS Registry no. :1276030-80-8

Tenofovir disoproxil maleate is a white to off white crystalline powder with solubility of 13.4 mg/ml in distilled water at 25°C and a partition co-efficient (log P) for tenofovir is 1.25 and the pKa is 3.75. The active pharmaceutical product is a single enantiomer that does not undergo racemisation either *in vitro* or *in vivo*.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

15/12/2016

10 DATE OF REVISION

20/09/2022

Summary Table of Changes

Section Changed	Summary of New Information
All	Change trade name from TENOFOVIR DISOPROXIL MYLAN to TENOFOVIR DISOPROXIL VIATRIS.
3, 6.1	Minor editorial changes

TENOFOVIR DISOPROXIL VIATRIS_pi\Sep22/00