NEW ZEALAND DATA SHEET

TENOFOVIR DISOPROXIL EMTRICITABINE EFAVIRENZ MYLAN

1. Product Name

Tenofovir disoproxil Emtricitabine Efavirenz Mylan, 300 mg/200 mg/600 mg film-coated tablets.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 300 mg tenofovir disoproxil maleate (equivalent to 245 mg tenofovir disoproxil), 200 mg emtricitabine and 600 mg efavirenz.

Tenofovir disoproxil Emtricitabine Efavirenz Mylan tables contain lactose. For the full list of excipients, see section 6.1.

Tenofovir disoproxil maleate 300mg is equivalent to tenofovir disoproxil fumarate 300 mg. Maleate and fumarate are isomers of each other. This data sheet makes reference to both the fumarate and maleate salt form.

3. Pharmaceutical Form

Each Tenofovir disoproxil Emtricitabine Efavirenz Mylan tablet is a pink film-coated, capsule shaped, biconvex tablet debossed with “M” on one side of the tablet and “TEE” on the other side.

4. Clinical Particulars

4.1 Therapeutic indications

Tenofovir disoproxil Emtricitabine Efavirenz Mylan is indicated for the treatment of HIV infected adults over the age of 18 years, alone or in combination with other antiretroviral agents.

4.2 Dose and method of administration

Adults

The recommended dose of Tenofovir disoproxil Emtricitabine Efavirenz Mylan is one tablet once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.

Special populations

Children and adolescents

Tenofovir disoproxil Emtricitabine Efavirenz Mylan is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Elderly

Tenofovir disoproxil Emtricitabine Efavirenz Mylan should be administered with caution to elderly patients (see section 4.4).

Renal impairment

Tenofovir disoproxil Emtricitabine Efavirenz Mylan is not recommended for patients with moderate or severe renal impairment (Creatinine Clearance (CrCl) < 50 mL/min). Patients with moderate or severe renal impairment require dose interval adjustments of tenofovir disoproxil fumarate and emtricitabine that cannot be achieved with the combination tablet (see section 4.4).

The safety and efficacy of once daily dosing of tenofovir disoproxil fumarate with emtricitabine in patients with mild renal impairment (CrCl 50 to 80 mL/min), have been demonstrated in clinical studies. No dosage adjustment is recommended for patients with renal impairment who receive efavirenz. Therefore no dosage adjustment is required for Tenofovir disoproxil Emtricitabine Efavirenz Mylan in patients with mild renal impairment.

Hepatic impairment

Tenofovir disoproxil Emtricitabine Efavirenz Mylan is not recommended for patients with moderate to severe hepatic impairment because of insufficient data to determine whether dose adjustment of efavirenz is necessary. Patients with mild hepatic impairment may be treated with Tenofovir disoproxil Emtricitabine Efavirenz Mylan, however caution should be exercised in administering Tenofovir disoproxil Emtricitabine Efavirenz Mylan to these patients (see section 4.4).

Where discontinuation of Tenofovir disoproxil Emtricitabine Efavirenz Mylan is necessary due to one of the components, or where dose modification is necessary, separate preparations of tenofovir disoproxil fumarate, emtricitabine and efavirenz are available. Please refer to the product information for these products.

4.3 Contraindications

Tenofovir disoproxil Emtricitabine Efavirenz Mylan is contraindicated in patients with known hypersensitivity to any of the active substances or any other component of the tablets (see section 6.1).

Tenofovir disoproxil Emtricitabine Efavirenz Mylan should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations (see section 4.5).

St John’s Wort

Tenofovir disoproxil Emtricitabine Efavirenz Mylan should not be used with St. John’s wort (*Hypericum perforatum*) or St. John’s wort-containing products since it is expected to result in reduced plasma concentrations of efavirenz. This effect is due to an induction of CYP3A4 and may result in loss of therapeutic effect and development of resistance.

4.4 Special warnings and precautions for use

Tenofovir disoproxil Emtricitabine Efavirenz Mylan is a fixed-dose combination of tenofovir disoproxil fumarate, emtricitabine and efavirenz and should not be administered concomitantly with other medicinal products containing any of the same active components, tenofovir disoproxil fumarate, emtricitabine, efavirenz, [unless dose-adjustment is required, e.g. with rifampicin (see section 4.5)], or with medicinal products containing lamivudine, tenofovir alafenamide or with adefovir dipivoxil.

General

Patients receiving tenofovir, emtricitabine and efavirenz 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, emtricitabine and efavirenz, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that tenofovir, emtricitabine and efavirenz is not a cure for HIV infection.

Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A4. Likewise, efavirenz may alter plasma concentrations of drugs metabolized by CYP3A4 or CYP2B6. The prominent effect of efavirenz at steady-state is induction of CYP3A4 and CYP2B6. However, efavirenz has demonstrated CYP3A4 inhibitory effects *in vitro*; therefore, the theoretical potential exists for efavirenz to increase the levels of CYP3A4 substrates. Caution should be used during the first days of tenofovir, emtricitabine and efavirenz therapy in patients taking a CYP3A4 substrate with both a narrow therapeutic index and the potential for serious and/or life-threatening adverse reactions (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression). Caution should be exercised for agents such as ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), midazolam, triazolam, bepridil, cisapride, and pimozide (see section 4.5).

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, including tenofovir disoproxil fumarate, alone or in combination with other antiretrovirals, in the treatment of HIV infection. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors.

Treatment with tenofovir, emtricitabine and efavirenz should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Renal impairment

Emtricitabine and tenofovir disoproxil fumarate are primarily excreted by the kidneys. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and Fanconi syndrome have been reported with the use of tenofovir disoproxil fumarate in clinical practice.

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy and, as clinically appropriate, during tenofovir, emtricitabine and efavirenz 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.

Tenofovir, emtricitabine and efavirenz is not recommended for patients with moderate or severe renal impairment (CrCl <50 mL/min). Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet.

Tenofovir, emtricitabine and efavirenz should be avoided with concurrent or recent use of a nephrotoxic agent.

Bone effects

Bone toxicity including a reduction in bone mineral density have been observed in tenofovir disoproxil fumarate studies in three animal species. Clinically relevant bone abnormalities have not been seen in long term clinical studies (>3 years) of tenofovir. However, bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8). If bone abnormalities are suspected during therapy then appropriate consultation should be obtained.

Liver disease

Tenofovir, emtricitabine and efavirenz is not recommended for patients with moderate or severe hepatic impairment because of insufficient data to determine whether dose adjustment of efavirenz is necessary. Because of the extensive cytochrome P450 (CYP450)-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution should be exercised in administering tenofovir, emtricitabine and efavirenz to patients with hepatic impairment. Patients should be monitored carefully for adverse events and, laboratory tests should be performed to evaluate their liver disease at periodic intervals.

In patients with underlying liver disease including hepatitis B or C infection and in patients treated with other medications associated with liver toxicity monitoring of liver enzymes is recommended. A few of the post-marketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors (see section 4.8). Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with tenofovir, emtricitabine and efavirenz needs to be weighed against the unknown risks of significant liver toxicity (see section 4.8).

HIV and hepatitis B virus (HBV) co-infection

Discontinuation of tenofovir, emtricitabine and efavirenz therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis due to emtricitabine and tenofovir disoproxil fumarate. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping tenofovir, emtricitabine and efavirenz treatment. If appropriate, initiation 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.

QTc prolongation

QTc prolongation has been observed with the use of efavirenz (see section 4.5). Consider alternatives to tenofovir, emtricitabine and efavirenz when co-administered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes.

Psychiatric symptoms

Serious psychiatric adverse reactions including severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behaviour, paranoid reactions and manic reactions have been reported in patients treated with efavirenz (see section 4.8). Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences. There have been reports (approximately 1 to 2 per 1000 efavirenz-treated patients) of delusions and inappropriate behaviour, predominately in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both efavirenz-treated and control-treated patients). There have been occasional post-marketing reports of death by suicide, delusions and psychosis-like behaviour; although a causal relationship to the use of efavirenz cannot be determined from these reports.

Patients should be advised that if they experience these symptoms they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of tenofovir, emtricitabine and efavirenz and if so, to determine whether the risks of continued therapy outweigh the benefits.

Nervous system symptoms

Symptoms including, but were not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported adverse events in patients receiving efavirenz 600 mg daily in clinical studies (see section 4.8). Nervous system symptoms usually begin during the first or second day of therapy and generally resolve after the first two to four weeks. Dosing at bedtime or on an empty stomach may improve the tolerability of these symptoms.

Patients should be informed that these common nervous system symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms. Patients receiving efavirenz should be alerted to the potential for additive central nervous system effects when efavirenz is used concomitantly with alcohol or psychoactive medicines.

Convulsions

Convulsions have been observed rarely in patients receiving efavirenz, including in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolised by the liver, such as carbamazepine, phenytoin and phenobarbitone, may require periodic monitoring of plasma levels (see section 4.5). Caution must be taken in any patients with a history of seizures.

Skin rash

Mild to moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of Grade 4 rashes (e.g. erythema multiforme or Stevens-Johnson syndrome) was approximately 0.14%. Efavirenz should be discontinued if severe rash associated with blistering, desquamation, mucosal involvement or fever develops. Efavirenz is not recommended for patients who have had a life threatening cutaneous reaction (e.g. Stevens-Johnson syndrome). Rash was reported in 59 of 182 children (32%) treated with efavirenz in three clinical trials for a median of 123 weeks and was severe in six patients.

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with efavirenz. In most patients, rash resolves with continuing therapy with efavirenz within one month. Tenofovir, emtricitabine and efavirenz can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when tenofovir, emtricitabine and efavirenz is restarted.

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited.

Lipodystrophy

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

Immune reconstitution syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tenofovir, emtricitabine and efavirenz. 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 jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders 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.

Effect of food

The administration of tenofovir, emtricitabine and efavirenz with food may increase efavirenz exposure (see section 5.2) and may lead to an increase in frequency of undesirable effects. It is recommended that tenofovir, emtricitabine and efavirenz be taken on an empty stomach, preferably at bedtime.

Special populations

Use in the elderly

Clinical studies of tenofovir disoproxil fumarate, emtricitabine and efavirenz did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Caution should be exercised when prescribing tenofovir, emtricitabine and efavirenz to the elderly, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

4.5 Interaction with other medicines and other forms of interaction

General

Any interactions that have been identified with tenofovir, emtricitabine and efavirenz individually may occur with combined tenofovir, emtricitabine and efavirenz therapy.

Tenofovir disoproxil fumarate and emtricitabine

Tenofovir and emtricitabine are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No medicine-medicine interactions due to competition for renal excretion have been observed; however, co-administration of tenofovir disoproxil fumarate and emtricitabine with medicines that are eliminated by active tubular secretion may increase serum concentrations of tenofovir, emtricitabine, and/or the co-administered medicine. Medicines that decrease renal function may increase serum concentrations of tenofovir and/or emtricitabine.

No clinically significant medicine interactions have been observed between tenofovir disoproxil fumarate and abacavir, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir, sofosbuvir and tacrolimus (see section 4.5) in studies conducted in healthy volunteers. 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 fumarate and ribavirin. Similarly, no clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, zidovudine and tenofovir disoproxil fumarate.

Efavirenz

The prominent effect of efavirenz at steady-state is induction of CYP3A and CYP2B6. Other compounds that are substrates of CYP3A4 or CYP2B6 may have decreased plasma concentrations when co-administered with efavirenz. Drugs that induce CYP3A4 activity may be expected to increase the clearance of efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits P450 isozymes 2C9, 2C19, and 3A4 in the range of observed efavirenz plasma concentrations.

Tenofovir, emtricitabine and efavirenz should not be administered concurrently with voriconazole or ergot derivatives (see section 4.3). Caution should be exercised when administering tenofovir, emtricitabine and efavirenz concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, bepridil, pimozide, voriconazole or ergot derivatives (see section 4.4).

Concomitant Antiretroviral Agents

Amprenavir

Although efavirenz (600 mg once daily) was seen to decrease the AUC, C_{max} and C_{min} of amprenavir (1200 mg every 12 hours) in HIV infected patients, the clinical significance of decreased amprenavir concentrations has not been established, the possibility of this interaction should be taken into consideration before choosing a regimen containing both efavirenz and amprenavir.

Fosamprenavir calcium

Appropriate doses of fosamprenavir (unboosted) and tenofovir, emtricitabine and efavirenz with respect to safety and efficacy have not been established. An additional 100 mg/day (300 mg total) of ritonavir is recommended when tenofovir, emtricitabine and efavirenz is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when tenofovir, emtricitabine and efavirenz is administered with fosamprenavir plus ritonavir twice daily.

Atazanavir/ritonavir

Insufficient data are available to make a dosing recommendation for atazanavir/ritonavir in combination of tenofovir, emtricitabine and efavirenz. Therefore co-administration of atazanavir/ritonavir and tenofovir, emtricitabine and efavirenz is not recommended.

Co-administration of efavirenz 600 mg with atazanavir in combination with low dose ritonavir resulted in substantial decreases in atazanavir exposure, necessitating dosage adjustment of atazanavir. Tenofovir disoproxil fumarate affects the pharmacokinetics of atazanavir (see Table 1). Tenofovir should only be administered with boosted atazanavir (ATZ 300 mg/RTV 100 mg). The safety and efficacy of this regimen has been substantiated over 48 weeks in a clinical study. When unboosted atazanavir (400 mg) was co-administered with tenofovir disoproxil fumarate, atazanavir increased tenofovir C_{max} by 14% and AUC by 24%.

Indinavir

Insufficient data are available to make a dosing recommendation with tenofovir, emtricitabine and efavirenz. When indinavir at an increased dose (1,000 mg every eight hours) was given with efavirenz, in uninfected volunteers, the indinavir AUC and C_{trough} were decreased on average by 33% to 46% and 39% to 57%, respectively,(ranges represent diurnal variation), compared to when indinavir was given alone at the standard dose (800 mg every 8 hours). Similar differences in indinavir AUC and C_{trough} were also observed in HIV infected patients who received indinavir (1000 mg every 8 hours) with efavirenz compared to indinavir given alone (800 mg every 8 hours). While the clinical significance of decreased indinavir concentrations has not been established, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both efavirenz and indinavir.

Lopinavir/ritonavir

Insufficient data are available to make a dosing recommendation with tenofovir, emtricitabine and efavirenz. When tenofovir disoproxil fumarate was administered with lopinavir (400 mg)/ritonavir (100 mg), the tenofovir AUC increased by 32%. Co-administration of lopinavir/ritonavir with efavirenz resulted in a substantial decrease in lopinavir exposure, necessitating dosage adjustment of lopinavir/ritonavir. When used in combination with efavirenz and two NRTIs in multiple protease inhibitor experienced subjects, increasing the dose of lopinavir/ritonavir 33.3% from 400/100 mg (three soft capsules) twice daily, to 533/133 mg (four soft capsules) twice daily yielded similar lopinavir plasma concentrations as compared to historical data of lopinavir/ritonavir 400/100 mg twice daily.

Raltegravir

The AUC, C_{max}, and C_{min} of raltegravir (400 mg single dose) were decreased by 36%, 36%, and 21%, respectively, when given with efavirenz (600 mg once daily) compared to raltegravir alone. The mechanism of the interaction is induction of the UGT1A1 enzyme by efavirenz. No dose adjustment is necessary for raltegravir.

Ritonavir

When efavirenz 600 mg (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) were studied in uninfected volunteers, the combination was not well tolerated and was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes).

Sufficient data on the tolerability of efavirenz with low-dose ritonavir (100 mg, once or twice daily) are not available. When using efavirenz in a regimen including low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, namely due to possible pharmacodynamic interaction.

Monitoring of liver enzymes is recommended when tenofovir, emtricitabine and efavirenz is used in combination with ritonavir.

Saquinavir

When saquinavir soft gelatin capsules (1,200 mg every eight hours) was given with efavirenz to uninfected volunteers, saquinavir AUC and C_{max} were decreased by 62% and 45 to 50%, respectively. Saquinavir should not be used as sole protease inhibitor in combination with tenofovir, emtricitabine and efavirenz. No data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir.

Didanosine

Concomitant dosing of tenofovir disoproxil fumarate with didanosine buffered tablets or enteric-coated capsules significantly increase the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. Table 1 below, summarises the effects of tenofovir disoproxil fumarate on the pharmacokinetics of didanosine.

As a result of this increased exposure, patients receiving tenofovir, emtricitabine, efavirenz and didanosine should be carefully monitored for didanosine-associated adverse events, including pancreatitis, lactic acidosis and neuropathy. Suppression of CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine at a dose of 400 mg daily. In adults weighing ≥ 60kg, the didanosine dose should be reduced to 250 mg daily when it is co-administered with tenofovir, emtricitabine and efavirenz. Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg. When co-administered, tenofovir, emtricitabine, efavirenz 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, emtricitabine and efavirenz should be under fasted conditions.

Co-administration of tenofovir, emtricitabine and efavirenz 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.

Table 1 Drug interactions: changes in pharmacokinetic parameters for didanosine and atazanavir in the presence of tenofovir DF.

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}
Didanosine[3] enteric-coated capsules	400 once/ with or without food[2]	26	↑48-64% (↑25- ↑89)	↑48-60% (↑31- ↑79)	NC
	250 once/ simulataneously with tenofovir DF, fasted[4]	28	↔	↑14 (0- ↑31)	NC
	250 once/ simulataneously with tenofovir DF, fed[2,4]	28	↓29 (↓39- ↓18)	↓11 (↓23- ↑2)	NC

Atazanavir sulfate[5]	400 once daily x 14 days	34	↓21 (↓27 to ↓14)	↓25 (↓30 to ↓19)	↓40 (↓48 to ↓32)
	Atazanavir/ritonavir[6] 300/100 once daily x 42 days	10	↓28 (↓50 to ↑5)[6]	↓25 (↓42 to ↓3)[6]	↓23 (↓46 to ↑10)[6]

1. Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. See section 4.4 regarding use of didanosine with tenofovir disoproxil fumarate.
4. Relative to 400 mg alone, fasted.
5. Reyataz (atazanavir) Prescribing Information (Bristol-Myers Squibb)
6. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} 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)

Maraviroc

The AUC_{12} and C_{max} of maraviroc (100 mg twice daily) are decreased by 45% and 51%, respectively, when given with efavirenz (600 mg once daily) compared to maraviroc administered alone. Refer to the prescribing information for maraviroc for guidance on co- administration of efavirenz. (Maraviroc is currently not available in New Zealand).

Hepatitis C antiviral agents

Boceprevir

The C_{min} of boceprevir (800 mg 3 times daily) was decreased by 44% when given with efavirenz (600 mg once daily) compared to boceprevir alone. The mechanism of the interaction is induction of CYP3A. Refer to the prescribing information for boceprevir for guidance on co-administration with efavirenz.

Telaprevir

Concomitant administration of telaprevir and efavirenz resulted in reduced steady- state exposures to telaprevir and efavirenz. When telaprevir 1125 mg every 8 hours was administered with efavirenz 600 mg once daily, the AUC, C_{max}, and C_{min} of telaprevir were decreased by 18%, 14%, and 25% relative to telaprevir 750 mg every 8 hours administered alone and the AUC, C_{max}, and C_{min} of efavirenz were decreased by 18%, 24%, and 10%. The mechanism of the effect on telaprevir is induction of CYP3A by efavirenz. Refer to the prescribing information for telaprevir for guidance on co-administration with efavirenz.

Simeprevir

Concomitant administration of simeprevir with efavirenz resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of simeprevir. Co-administration of simeprevir with tenofovir, emtricitabine and efavirenz is not recommended. Refer to the prescribing information for simeprevir for more information.

Ledipasvir/sofosbuvir

Concomitant administration of ledipasvir/sofosbuvir with tenofovir, emtricitabine and efavirenz resulted in increases in tenofovir AUC, C_{max} and C_{min} of approximately 98%, 79% and 163%, respectively, compared with tenofovir, emtricitabine and efavirenz alone. No dose adjustment of tenofovir, emtricitabine and efavirenz or ledipasvir/sofosbuvir is required. Patients receiving tenofovir, emtricitabine and efavirenz with ledipasvir/sofosbuvir should be monitored for adverse reactions associated with tenofovir disoproxil fumarate.

Sofosbuvir

Concomitant administration of sofosbuvir with tenofovir, emtricitabine and efavirenz resulted in increases in tenofovir C_{max} by 25%, compared with tenofovir, emtricitabine and efavirenz alone.

Tenofovir AUC and C_{min} were unaltered by sofosbuvir co-administration. No dose adjustment of tenofovir, emtricitabine and efavirenz or sofosbuvir is required.

Sofosbuvir / velpatasvir

Concomitant administration of sofosbuvir/velpatasvir with tenofovir, emtricitabine and efavirenz increased tenofovir AUC, C_{max} , and C_{min} by 81%, 77%, and 121%, respectively, compared with tenofovir, emtricitabine and efavirenz alone, and decreased velpatasvir AUC, C_{max}, and C_{min} by 53%, 47% and 57%, compared with sofosbuvir/velpatasvir alone. Co-administration of tenofovir, emtricitabine and efavirenz with sofosbuvir/velpatasvir is not recommended.

Concomitant antimicrobial agents

Macrolide antibiotics

Clarithromycin

Co-administration of efavirenz 400 mg once daily with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and C_{max} of clarithromycin decreased 39 and 26%, respectively, while the AUC and C_{max} of the active clarithromycin hydroxymetabolite were increased 34 and 49%, respectively, when used in combination with efavirenz. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin should be considered.

Rifamycins

Rifabutin

Co-administration of rifabutin (300 mg once daily for 14 days) and efavirenz (600 mg once daily for 14 days) in uninfected volunteers, reduced the C_{max} and AUC of rifabutin by 32% and 38% respectively. Rifabutin clearance was increased when rifabutin was given with efavirenz. The daily dose of rifabutin should be increased by 50% when co-administered with tenofovir, emtricitabine and efavirenz. For regimens where rifabutin is given 2 or 3 times a week, a doubling of the rifabutin dose should be considered. The possibility of this interaction should been taken into consideration before choosing a regimen containing both efavirenz and rifabutin.

Rifampicin

Rifampicin reduced efavirenz AUC by 26% and C_{max} by 20% in uninfected volunteers. An additional 200 mg/day (total 800 mg/day) of efavirenz is recommended when rifampicin is co-administered with tenofovir, emtricitabine and efavirenz to patients weighing 50 kg or more.

Concomitant antifungal agents

Itraconazole

Co-administration of efavirenz (600 mg once daily) with itraconazole (200 mg orally every 12 hours) in uninfected volunteers decreased the steady-state AUC, C_{max} and C_{min} of itraconzole. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

Voriconazole

Voriconazole increased efavirenz AUC and C_{max} by 44% and 38%, respectively while efavirenz decreased voriconazole AUC and C_{max} by 77% and 61% respectively in uninfected volunteers. Co-administration of tenofovir, emtricitabine, efavirenz and voriconazole is contraindicated (see section 4.3).

Posaconazole

Co-administration of efavirenz (400 mg orally once daily) with posaconazole (400 mg orally twice daily) decreased the AUC and C_{max} of posaconazole by 50% and 45% respectively, compared to posaconazole administered alone. Concomitant use of posaconazole, tenofovir, emtricitabine and efavirenz should be avoided unless the benefit to the patient outweighs the risk.

Antimalarial agents

Artemether/lumefantrine

Co-administration of efavirenz (600 mg once daily) with artemether 20 mg/lumefantrine 120 mg tablets (6 4-tablet doses over 3 days) resulted in a decrease in exposures (AUC) to artemether, dihydroartemisinin (active metabolite of artemether), and lumefantrine by approximately 51%, 46%, and 21%, respectively. Exposure to efavirenz was not significantly affected. Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when tenofovir, emtricitabine and efavirenz and artemether/lumefantrine tablets are co-administered.

Atovaquone/proguanil

Efavirenz (600 mg once daily) was co-administered with atovaquone and proguanil 250/100 mg to HIV-infected and healthy subjects. After adjustment for potential confounding parameters (race, age, smoking status, body weight and height, CYP2C19 genotype) in the multiple variable linear regression analysis, geometric mean atovaquone AUC and C_{max} were reduced 75% and 44%, respectively, while proguanil AUC was reduced approximately 43%. Reduced therapeutic effect of antimalarial drugs may result from the substantial decrease in plasma concentrations of atovaquone. Co-administration of atovaquone/proguanil with tenofovir, emtricitabine and efavirenz should be avoided whenever possible.

Concomitant anticonvulsant agents

Carbamazepine

Co-administration of efavirenz (600 mg orally once daily) with carbamazepine (400 mg once daily) in uninfected volunteers resulted in a two-way interaction. The steady-state AUC, C_{max} and C_{min} of carbamazepine decreased by 27%, 20% and 35% respectively, while the steady-state AUC, C_{max} and C_{min} of efavirenz decreased by 36%, 21% and 47% respectively. The steady-state AUC, C_{max} and C_{min} of the active carbamazepine epoxide metabolite remained unchanged. Carbamazepine plasma levels should be monitored periodically. There are no data on the co-administration of higher doses of either medicinal product; therefore, no dose recommendation can be made, and alternative anticonvulsant treatment should be considered.

Other anticonvulsants

When efavirenz is administered concomitantly with phenytoin, phenobarbitone or other anticonvulsants that are substrates of CYP450 isozymes, there is the potential for reduction or increase in the plasma concentrations of each agent; therefore, periodic monitoring of plasma levels should be conducted.

Lipid-lowering agents

Co-administration of efavirenz with the HMG-CoA reductase inhibitors atorvastatin, pravastatin, or simvastatin has been shown to reduce the plasma concentration of the statin in uninfected volunteers. Dosage adjustments of statins may be required (refer to the data sheet for the statin).

Atorvastatin

Co-administration of efavirenz (600 mg orally once daily) with atorvastatin (10 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of atorvastatin by 43% and 12%, respectively, of 2-hydroxy atorvastatin by 35% and 13% respectively, of 4-hydroxy atorvastatin by 4% and 47%, respectively, and of total active HMG-CoA reductase inhibitors by 34% and 20%, respectively, compared to atorvastatin administered alone.

Pravastatin

Co-administration of efavirenz (600 mg orally once daily) with pravastatin (40 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of pravastatin by 40% and 18% respectively, compared to pravastatin administered alone.

Simvastatin

Co-administration of efavirenz (600 mg orally once daily) with simvastatin (40 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of simvastatin by 69% and 76% respectively; of simvastatin acid by 58% and 51% respectively; of total active HMG-CoA reductase inhibitors by 60% and 62% respectively; of total HMG-CoA reductase inhibitors by 60% and 70% respectively compared to simvastatin administered alone.

Co-administration of efavirenz with atorvastatin, pravastatin or simvastatin did not affect the efavirenz AUC or C_{max} values. No dosage adjustment is necessary for efavirenz.

Concomitant calcium channel blockers

Diltiazem

Co-administration of efavirenz (600 mg orally once daily) with diltiazem (240 mg orally once daily) in uninfected volunteers decreased the steady-state AUC, C_{max} and C_{min} of diltiazem by 69%, 60% and 63% respectively; desacetyl diltiazem by 75%, 64% and 62% respectively and N-monodesmethyl diltiazem by 37%, 28% and 37% respectively, compared to diltiazem administered alone. Diltiazem dose adjustments should be guided by clinical response (refer to the data sheet for diltiazem). Pharmacokinetic parameters for efavirenz were slightly increased (11% to 16%). No dosage adjustment of efavirenz is necessary when administered with diltiazem.

Other calcium channel blockers: No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A4 enzyme (e.g. verapamil, felodipine, nifedipine). When efavirenz is administered concomitantly with one of these agents, there is potential for reduction in the plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the data sheet for the calcium channel blocker).

Other Interactions

<u>Antidepressants</u>

Sertraline

The C_{max}, C_{24} and AUC of sertraline were decreased when given with efavirenz. The possibility of this interaction should be taken into consideration before choosing a regimen containing both efavirenz and sertraline. Sertraline dose increases should be guided by clinical response.

Bupropion

Co-administration of efavirenz (600 mg orally once daily) with bupropion (150 mg single dose, sustained release) in uninfected volunteers decreased the AUC and C_{max} of bupropion by 55% and 34%, respectively, compared to bupropion alone. Hydroxybupropion AUC was unchanged and hydroxybupropion C_{max} was increased by 50%. The effect of efavirenz on bupropion exposure is thought to be due to the induction of bupropion metabolism. Increases in bupropion dose may be necessary when taken in combination with efavirenz and should be guided by clinical response, but should not exceed the maximum recommended dose. No adjustment of efavirenz is required.

<u>Narcotic analgesics</u>

Methadone

Co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal in a study of HIV-infected patients with a history of injection drug use. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

Immunosuppressants

When an immunosuppressant metabolized by CYP3A4 (e.g. cyclosporine, tacrolimus, or sirolimus) is administered with efavirenz, decreased exposure of the immunosuppressant may be expected due to CYP3A4 induction. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with tenofovir, emtricitabine and efavirenz. Immunosuppressants metabolized by CYP3A4 are not anticipated to affect exposure of efavirenz. There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate plus emtricitabine was co-administered with tacrolimus.

Hormonal contraceptives

A reliable method of barrier contraception must be used in addition to hormonal contraceptives.

Oral

When an oral contraceptive (ethinyl estradiol 0.035 mg/norgestimate 0.25 mg once daily) and efavirenz (600 mg once daily) were co-administered for 14 days, efavirenz had no effect on ethinyl estradiol concentrations but plasma concentrations of norelgestromin and levonorgestrel, active metabolites of norgestimate, were markedly decreased in the presence of efavirenz (64%, 46%, and 82% decrease in norelgestromin AUC, C_{max} and C_{min}, respectively, and 83%, 80% and 86% decrease in levonorgestrel AUC, C_{max} and C_{min}, respectively). The clinical significance of these effects is not known. No effect of ethinylestradiol on efavirenz plasma concentrations was observed.

Implant

The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected (CYP3A4 induction), and there have been occasional post-marketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.

St. John's wort

(*Hypericum perforatum*): See section 4.3.

Cannabinoid test interaction

Efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV infected subjects receiving efavirenz. Confirmation of positive screening tests for cannabinoids by a more specific method such as gas chromatography/mass spectrometry is recommended.

QT prolonging drugs

There is limited information available on the potential for a pharmacodynamic interaction between efavirenz and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of efavirenz (see section 5). Consider alternatives to tenofovir, emtricitabine and efavirenz when co-administered with a drug with a known risk of Torsade de Pointes.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category D

Efavirenz may cause foetal harm when administered during the first trimester to a pregnant women. Pregnancy should be avoided in women receiving tenofovir, emtricitabine and efavirenz. Barrier contraception must always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of tenofovir, emtricitabine and efavirenz. If a woman takes tenofovir, emtricitabine and efavirenz during the first trimester of pregnancy, or becomes pregnant whilst taking tenofovir, emtricitabine and efavirenz, she should the informed of the potential harm to the foetus. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of tenofovir, emtricitabine and efavirenz is recommended.

There are no well controlled clinical studies of tenofovir, emtricitabine and efavirenz in pregnant women. No embryofoetal development studies have been conducted with tenofovir disoproxil fumarate, emtricitabine and efavirenz in combination. Tenofovir, emtricitabine and efavirenz should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus and there are no other appropriate treatment options.

In post-marketing experience through an antiretroviral pregnancy registry, more than 750 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been reported with no specific malformation pattern. Retrospectively in this registry, a small number of neural tube defects, including meningomyelocele, have been reported; but causality has not been established.

Efavirenz

Malformations have been observed in 3 of 20 foetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital days 20 to 150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those seen in humans given 600 mg/day. Anencephaly and unilateral anophthalmia were observed in one foetus, microophthalmia was observed in another foetus, and cleft palate was observed in a third foetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces foetal blood concentrations similar to maternal blood concentrations. Because teratogenic effects have been seen in primates at efavirenz exposures similar to those seen in the clinic at the recommended dose, pregnancy should be avoided in women receiving efavirenz.

Efavirenz has been shown to cross the placenta in rats and rabbits and produces foetal blood concentrations of efavirenz similar to maternal blood concentrations. An increase in foetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given efavirenz 600 mg once daily. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to, and AUC values approximately half of, those achieved in humans when given efavirenz 600 mg once daily.

Breast-feeding

Efavirenz

Studies in rats have demonstrated that efavirenz is secreted into the milk of lactating rats; concentrations of efavirenz were eight times higher than those in maternal plasma. Efavirenz has also been shown to pass into human breast milk.

Tenofovir disoproxil fumarate

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 disoproxil fumarate are unknown.

Emtricitabine

Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the emtricitabine IC_{50} but 3 to 12 times lower than the C_{min} (minimal expected trough concentration in adults) achieved from oral administration of emtricitabine. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Because of the potential for both HIV transmission and for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving tenofovir, emtricitabine and efavirenz.

Fertility

No reproductive toxicity studies have been conducted with tenofovir disoproxil fumarate, emtricitabine and efavirenz in combination. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

Tenofovir, emtricitabine and efavirenz may cause dizziness, impaired concentration and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Adverse events associated with the individual antiretroviral agents of tenofovir, emtricitabine and efavirenz, may be expected to occur with the fixed combination tablet.

For additional safety information about tenofovir disoproxil fumarate, emtricitabine or efavirenz in combination with other antiretroviral agents, consult the data sheet for these products.

In addition to the adverse events in Study 934 (Table 2) and Study 073, the following adverse events were observed in clinical studies of tenofovir disoproxil fumarate, emtricitabine or efavirenz in combination with other antiretroviral agents.

Tenofovir disoproxil fumarate

More than 12,000 patients have been treated with tenofovir disoproxil fumarate 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 fumarate 300 mg once daily in Phase I-III clinical trials; over 11,000 patients have received tenofovir disoproxil fumarate in expanded access studies.

The most common adverse events that occurred in patients receiving tenofovir disoproxil fumarate with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhoea, vomiting and flatulence.

Emtricitabine

More than 2000 adult patients with HIV infection have been treated with emtricitabine alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in Phase I-III clinical trials.

Assessment of adverse reactions is based on data from studies 301A and 303 in which 571 treatment naïve (301A) and 440 treatment experienced (303) patients received emtricitabine 200 mg (n=580) or comparator drug (n=431) for 48 weeks.

The most common adverse events that occurred in patients receiving emtricitabine with other antiretroviral agents in clinical trials were headache, diarrhoea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All adverse events were reported with similar frequency in emtricitabine and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the emtricitabine treated group.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

In addition to the adverse reactions reported in adults, anaemia has been reported commonly and hyperpigmentation very commonly, in paediatric patients.

Efavirenz

Efavirenz was generally well tolerated in clinical trials. Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 patients who received efavirenz 600 mg daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported undesirable effects of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). The most significant adverse events observed in patients treated with efavirenz are nervous system symptoms, psychiatric symptoms, and rash (see section 4.4).

Psychiatric symptoms (see section 4.4): Serious psychiatric adverse reactions have been reported in patients treated with efavirenz. In controlled trials of 1008 adults treated with regimens containing efavirenz for an average of 1.6 years and 635 adults treated with control regimens for an average of 1.3 years, the frequency of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were severe depression (1.6%, 0.6%), suicidal ideation (0.6%, 0.3%), nonfatal suicide attempts (0.4%, 0%), aggressive behaviour (0.4%, 0.3%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.1%, 0%). Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences, with the frequency of each of the above events ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation. There have also been occasional post-marketing reports of death by suicide, delusions, and psychosis-like behaviour, although a causal relationship to the use of efavirenz cannot be determined from these reports.

Nervous system symptoms (see section 4.4): Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration, abnormal dreaming, agitation, euphoria, amnesia, stupor, abnormal thinking, and depersonalization, are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies. In controlled clinical studies where 600 mg efavirenz was administered with other antiretroviral agents, 19.4% of patients experience nervous system symptoms of moderate-to-severe intensity compared to 9.0% of patients receiving control regimens. These symptoms were severe in 2.0% of patients receiving efavirenz 600 mg daily and in 1.3% of patients receiving control regimens. In clinical studies, 2.1% of patients treated with 600 mg of efavirenz discontinued therapy because of nervous system symptoms.

Nervous system symptoms usually begin during the first 1-2 days of therapy and generally resolve after the first 2-4 weeks. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing efavirenz, and from 3% to 5% in patients treated with a control regimen. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. Dosing at bedtime or on an empty stomach may improve the tolerability of these symptoms (see section 4.2). Dose reduction or splitting the daily dose has not been shown to provide benefit and is not recommended.

Rash (see section 4.4): In clinical studies, 26% of patients treated with 600 mg of efavirenz experience skin rash compared with 17% of patients treated in control groups. Skin rash was considered treatment related in 18% of patients treated with efavirenz. Severe rash occurred in less than 1% of patients treated with efavirenz, and 1.7% discontinued therapy because of rash. The incidence of erythema multiforme or Steven-Johnson syndrome was approximately 0.1%.

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz. In most patients, rash resolves with continuing therapy with efavirenz within 1 month. Tenofovir, emtricitabine and efavirenz can be reinitiated in patients who interrupted therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when tenofovir, emtricitabine and efavirenz is restarted.

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with efavirenz. Mild-to-moderate rash developed in nine of these patients while receiving therapy with efavirenz, and two discontinued because of rash.

Other, less frequent, clinically significant treatment related undesirable effects reported in all clinical trials include: allergic reaction, hypersensitivity, abnormal coordination, ataxia, confusion, stupor, vertigo, vomiting, diarrhoea, hepatitis, impaired concentration, insomnia, anxiety, abnormal dreams, somnolence, depression, abnormal thinking, agitation, amnesia, delirium, emotional lability, euphoria, hallucination and psychosis.

A few cases of pancreatitis has been reported, although a causal relationship with efavirenz has not been established.

Clinical trials

Tenofovir disoproxil fumarate + Emtricitabine + Efavirenz

Study 934

Study 934 was an open-label active-controlled study in which 511 antiretroviral-naïve patients received either tenofovir disoproxil fumarate, emtricitabine and efavirenz in combination (n=257) or 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 2). Adverse events leading to study drug discontinuation occurred in significantly smaller number of patients in the fixed dose tenofovir disoproxil 300mg/emtricitabine 200 mg group compared to the lamivudine/zidovudine 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 fixed dose tenofovir disoproxil 300mg/emtricitabine 200mg group and 6% of patients in the lamivudine/zidovudine group.

Table 2. Selected treatment-emergent adverse reactions[1] (grades 2-4) reported in ≥ 5% in any treatment group in study 934 (0-144 weeks)

	Tenofovir/ emtricitabine[2] + efavirenz (N=257)	Lamivudine/ zidovudine + efavirenz (N=254)
Gastrointestinal disorders		
Diarrhoea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General disorders and administration site condition		
Fatigue	9%	8%
Infections and infestations		
Sinusitis	8%	4%
Upper respiratory tract infections	8%	5%
Nasopharyngitis	5%	3%
Nervous system disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric disorders		
Depression	9%	7%
Insomnia	5%	7%
Skin and subcutaneous tissue disorders		
Rash[3]	5%	4%

1. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
2. Patients received emtricitabine + tenofovir disoproxil fumarate up to week 96 and switched to tenofovir disoproxil fumarate/emtricitabine from week 96 to 144.
3. Rash event includes rash, exfoliative rash, rash generalised, rash macular, rash maculo-papular, rash pruritic and rash vesicular

Study 073

In Study 073, patients with stable, virologic suppression on antiretroviral therapy and no history of virologic failure were randomised to receive tenofovir emtricitabine efavirenz or to stay on their baseline regimen. The adverse reactions observed in Study 073 were generally consistent with those seen in Study 934 and those seen with the individual components of tenofovir emtricitabine efavirenz when each was administered in combination with other antiretroviral agents.

Laboratory abnormalities

Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 3).

Table 3. Grade 3/4 laboratory abnormalities reported in >1% of patients in either treatment group study 934 (0–144 weeks)

	Tenofovir/ emtricitabine[1] + efavirenz (N=254)	Lamivudine/ zidovudine + efavirenz (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 emtricitabine + tenofovir disoproxil fumarate up to week 96 and switched to Tenofovir disoproxil fumarate/emtricitabine from week 96 to 144.

Laboratory abnormalities observed in Study 073 were generally consistent with those in Study 934.

Post-marketing surveillance

In addition to adverse events reported from clinical trials, the following events have been reported in post marketing surveillance. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Tenofovir disoproxil fumarate

Immune system disorders

Allergic reaction (including angioedema).

Metabolism and nutrition disorders

Hypokaleamia, hypophosphataemia, lactic acidosis.

Respiratory, thoracic and mediastinal disorders

Dyspnoea.

Gastrointestinal disorders

Increased amylase, abdominal pain, pancreatitis.

Hepoatobiliary disorders

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

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 administration site conditions

Asthaenia.

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 fumarate therapy in the absence of proximal renal tubulopathy.

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).

Exacerbations of hepatitis after discontinuation of treatment

In HIV infected patients co- infected with HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment (see section 4.4).

Emtricitabine

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).

Efavirenz

Psychiatric disorders

Completed suicide, paranoid reaction, psychosis, delusion, neurosis, catatonia.

Nervous system disorders

Convulsions, cerebellar coordination and balance disturbances, tremor.

Eye disorders

Blurred vision.

Ear and labyrinth disorders

Tinnitus.

Gastrointestinal disorders

Abdominal pain, pancreatitis.

Hepatobiliary disorders

Hepatic failure.

Skin and subcutaneous tissue disorders

Pruritus, photoallergic dermatitis, redistribution/accumulation of body fat in areas such as the back of the neck, breasts, abdomen and retroperitoneum.

Vascular disorders

Flushing.

Reproductive system and breast disorders

Gyneocomastia.

A few of the post-marketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

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).

Use in children

Tenofovir emtricitabine efavirenz is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Undesirable effects with an altered frequency have been observed in paediatric patients following the administration of efavirenz or emtricitabine.

Undesirable effects in children receiving efavirenz were generally similar to those of adult patients; however, rash was reported more frequently in children and was more often of higher grade than in adults. Rash was reported in 59 of 182 children (32%) treated with efavirenz.

In addition to the adverse reactions reported in adults, anaemia was common and hyperpigmentation was very common in paediatric patients receiving emtricitabine in a clinical study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Treatment of overdose with Tenofovir disoproxil Emtricitabine Efavirenz Mylan should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. There is no specific antidote for overdose with efavirenz. Haemodialysis can remove both tenofovir disoproxil fumarate and emtricitabine (refer to detailed information below). However, since efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of it from blood.

Tenofovir disoproxil fumarate

Clinical experience of doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available from two studies. In one study, intravenous tenofovir, equivalent to 16.7 mg/kg/day of tenofovir disoproxil fumarate, was administered daily for 7 days. In the second study, 600 mg of tenofovir disoproxil 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. Tenofovir is efficiently removed by haemodialysis; with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour haemodialysis studied session removed approximately 10% of the administered tenofovir dose.

Emtricitabine

Limited clinical experience is available at doses higher than the therapeutic dose of tenofovir disoproxil fumarate/emtricitabine. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported. The effects of higher doses are not known.

Haemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Efavirenz

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations; ATC code: J05AR06.

Mechanism of action

Tenofovir disoproxil maleate

Is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil maleate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of human immunodeficiency virus-type 1 (HIV-1) reverse transciptase (RT) by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into deoxyribonucleic acid (DNA), by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Emtricitabine

A synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′- triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε and mitochondrial DNA polymerase γ.

Efavirenz

Is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 RT with respect to template, primer or nucleoside triphosphates, with a small component of competitive inhibition. Human immunodeficiency virus-type 2 (HIV-2) RT and human cellular DNA polymerases (α, β, γ, and δ) are not inhibited by concentrations of efavirenz well in excess of those achieved clinically.

Cardiac electrophysiology

The effect of efavirenz on the QTc interval was evaluated in an open-label, positive and placebo-controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean C_{max} of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean C_{max} observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 msec and 11.3 msec, respectively, in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see section 4.4).

Pharmacodynamic effects

Antiviral activity in vitro

Tenofovir disoproxil fumarate, emtricitabine and efavirenz

In combination studies evaluating the *in vitro* antiviral activity of emtricitabine and efavirenz together, efavirenz and tenofovir together and emtricitabine and tenofovir together, additive to synergistic antiviral effects were observed.

Tenofovir disoproxil fumarate

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04 to 8.5 µM. In drug combination studies of tenofovir with nucleoside analogue reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC50 values ranged from 0.5 to 2.2 µM). In addition, tenofovir has also been shown to be active *in vitro* against HIV-2, with similar potency as observed against HIV-1.

Emtricitabine

The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC50 value for emtricitabine was in the range of 0.0013 to 0.64 µM (0.0003 to 0.158 µg/mL). In drug combination studies of emtricitabine with NRTIs (abacavir, lamivudine, stavudine, zalcitabine, zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, C, D, E, F, and G (IC_{50} values ranged from 0.007 to 0.075 µM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 µM)

Efavirenz

The *in vitro* antiviral activity of efavirenz was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures enriched from PBMCs. The 90 to 95% inhibitory concentration (IC_{90} to IC_{95}) of efavirenz for wild-type laboratory adapted strains and clinical isolates ranged from 1.7 to less than or equal to 25 nM. Efavirenz demonstrated synergistic activity in cell culture in combination with the NRTIs zidovudine or didanosine, or the protease inhibitor, indinavir.

Anti-hepatitis B virus activity *in vitro*

In vitro studies evaluating the HBV activity of tenofovir, emtricitabine and efavirenz and efavirenz have not been conducted.

Tenofovir disoproxil fumarate and emtricitabine

Tenofovir inhibits HBV production in HepG2 2.2.15 with an IC_{50} value of 1.1µM. Emtricitabine inhibits HBV production against laboratory strains of HBV with IC_{50} values in the range of 0.01 to 0.04 µM.

Drug resistance

Tenofovir disoproxil fumarate, emtricitabine and efavirenz

HIV isolates with reduced susceptibility to the combination of tenofovir, emtricitabine and efavirenz have been selected in cell culture and in clinical studies. Genotypic analysis of these isolates identified the K103N, M184V/I and/or the K65R amino acid substitutions in the viral RT.

Tenofovir disoproxil fumarate

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2 to 4 fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir disoproxil fumarate in combination with other antiretroviral agents. In treatment-naïve patients treated with tenofovir disoproxil fumarate + lamivudine + efavirenz through 144 weeks, viral isolates from 8/47 (17%) patients with virologic failure showed reduced susceptibility to tenofovir. In treatment-naïve patients treated with tenofovir disoproxil fumarate + emtricitabine + efavirenz through 144 weeks, none of the HIV isolates from 19 patients analysed for resistance showed reduced susceptibility to tenofovir or the presence of the K65R mutation. In treatment-experienced patients, 14/304 (4.6%) of the tenofovir disoproxil fumarate-treated patients with virologic failure showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed the K65R mutation in the HIV-1 reverse transcriptase gene.

Emtricitabine

Emtricitabine-resistant isolates of HIV have been selected *in vitro.* Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 37.5% of treatment-naïve patients with virologic failure showed reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV reverse transcriptase gene. In a second study in treatment-naïve patients, genotyping of viral isolates from 2/12 (17%) patients showed development of the M184V/I mutation.

Efavirenz

The potency of efavirenz in cell culture against viral variants with amino acid substitutions at positions 48, 108, 179, 181 or 236 in RT or variants with amino acid substitutions in the protease was similar to that observed against wild type viral strains. The single substitutions which led to the highest resistance to efavirenz in cell culture correspond to a leucine to isoleucine change at position 100 (L100I, 17 to 22-fold resistance) and a lysine to asparagine at position 103 (K103N, 18 to 33-fold resistance). Greater than 100-fold loss of susceptibility was observed against HIV variants expressing K103N in addition to other amino acid substitutions in RT. K103N was the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during clinical studies of efavirenz in combination with indinavir or zidovudine + lamivudine. This mutation was observed in 90% of patients receiving efavirenz with virological failure. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. The pattern of amino acid substitutions in RT associated with resistance to efavirenz was independent of the other antiviral medications used in combination with efavirenz.

In a clinical study of treatment-naïve patients (Study 934, see section 5.1; clinical efficacy and safety) resistance analysis was performed on HIV isolates from all virologic failure patients with confirmed HIV RNA > 400 copies/ml at week 144 while on study drug or after treatment switch. Genotypic resistance to efavirenz, predominantly the K103N substitution, was the most common form of resistance that developed. Resistance to efavirenz occurred in 68% (13/19) analysed patients in the fixed dose tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg group and in 72% (21/29) analysed patients in the lamivudine/zidovudine group.

Cross-resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognised.

Tenofovir disoproxil fumarate

The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours the K65R mutation. The K70E substitution selected by tenofovir DF results in reduced susceptibility to abacavir, didanosine, emtricitabine and lamivudine. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil fumarate. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Emtricitabine

Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation associated with resistance to NNRTIs was susceptible to emtricitabine.

Efavirenz

Cross-resistance profiles for efavirenz, nevirapine and delavirdine in cell culture demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs. Two of three delavirdine resistant clinical isolates examined were cross resistant to efavirenz and contained the K103N substitution. A third isolate which carried a substitution at position 236 of RT was not cross resistant to efavirenz. Viral isolates recovered from PBMCs of patients enrolled in efavirenz clinical trials who showed evidence of treatment failure (viral load rebound) were assessed for susceptibility to NNRTIs. Thirteen isolates previously characterised as efavirenz resistant were also resistant to nevirapine and delavirdine. Five of these NNRTI resistant isolates were found to have K103N or a valine to isoleucine substitution at position 108 (V108I) in RT. Three of the efavirenz treatment failure isolates tested remained sensitive to efavirenz in cell culture and were also sensitive to nevirapine and delavirdine.

The potential for cross resistance between efavirenz and PIs is low because of the different enzyme targets involved. The potential for cross resistance between efavirenz and NRTIs is low because of the different binding sites on the target and mechanism of action.

Clinical efficacy and safety

The data available to support the efficacy of tenofovir disoproxil fumarate, emtricitabine and efavirenz tablets include the available data for each individual agent, the data from clinical study 934 where the three agents were used concurrently, clinical study 073 where tenofovir disoproxil fumarate, emtricitabine and efavirenz was used in antiretroviral treatment experienced patients and the demonstration of bioequivalence between tenofovir disoproxil fumarate, emtricitabine and efavirenz tablets and the three individual agents co-administered under fasting conditions.

Study 934: Tenofovir disoproxil fumarate + emtricitabine + efavirenz compared with lamivudine / zidovudine + efavirenz

Study 934 is a randomized, 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 emtricitabine + tenofovir disoproxil fumarate administered in combination with efavirenz or lamivudine/zidovudine administered in combination with efavirenz. For patients randomized to receive emtricitabine + tenofovir disoproxil fumarate the two medicines were administered individually for the first 96 weeks and then switched to fixed dose combination tenofovir disoproxil 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 Cockroft-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 medicines 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/mm3 (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 4.

Table 4. 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	
	Emtricitabine + tenofovir + efavirenz (N=244)	Lamivudine/ zidovudine + efavirenz (N=243)	Tenofovir/ emtricitabine[4] + efavirenz (N=227)	Lamivudine/ zidovudine + efavirenz (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 emtricitabine + tenofovir up to week 96 and switched to tenofovir/emtricitabine from week 96 to 144.

In this study, tenofovir disoproxil fumarate, emtricitabine and efavirenz in combination was statistically significantly superior to lamivudine/zidovudine in combination with efavirenz with regards to the primary and secondary endpoints: in achieving and maintaining HIV-1 RNA < 400 copies/mL through 48 and 144 weeks (Table 4). The difference in the proportions of responders between the tenofovir disoproxil fumarate + emtricitabine group and the lamivudine/zidovudine 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 fumarate + emtricitabine and the lamivudine/zidovudine arms, respectively, achieved and maintained HIV-1 RNA <50 copies/mL. The difference in the proportions of responders between the tenofovir disoproxil fumarate + emtricitabine group and the lamivudine/zidovudine 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 fixed dose combination tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg group (64%) compared with the lamivudine/zidovudine 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 fumarate + emtricitabine + efavirenz arm, and 158 cells/mm^3 and 271 cells/mm^3 for the lamivudine/zidovudine + 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 fixed dose combination tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg group and in 72% (21/29) analysed patients in the lamivudine/zidovudine group.

The M184V mutation, associated with resistance to emtricitabine and lamivudine, developed significantly less in the analysed patients in the fixed dose combination tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg group 11% (2/19) compared with the analysed patients in the lamivudine/zidovudine group, 34% (10/29). Two patients in the lamivudine/zidovudine 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 disoproxil fumarate.

Study 073: Tenofovir disoproxil fumarate + emtricitabine + efavirenz compared to stable baseline regimen (combination therapy)

Study 073 was a 48 week open-label, randomised clinical study in patients with stable, virologic suppression on combination antiretroviral therapy. The study compared the efficacy of tenofovir disoproxil fumarate + emtricitabine + efavirenz to antiretroviral therapy consisting of at least two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a protease inhibitor (with or without ritonavir) or a non-nucleoside reverse transcriptase inhibitor. At baseline, patients had been virologically suppressed (HIV-1 RNA < 200 copies/mL) on their current antiretroviral therapy for at least 12 weeks prior to study entry, and had no known HIV-1 substitutions conferring resistance to the components of tenofovir disoproxil fumarate + emtricitabine + efavirenz or history of virologic failure. Assessments were also included to evaluate change in HIV symptom index, quality of life, medication preference, and adherence.

Patients were randomised to switch to tenofovir disoproxil fumarate + emtricitabine + efavirenz (N=203) or stay on their baseline regimen (SBR) (N=97). Patients had a mean age of 43 years (range 22 to 73 years), 88% were male, 68% were white, 29% were black, and 3% were of other races. At baseline, median CD4 cell count was 516 cells/mm3 and all but 11 patients (3.7%) had HIV-1 RNA < 50 copies/mL. The median time since onset of antiretroviral therapy was three years.

The primary efficacy endpoint was the maintenance of confirmed HIV-1 RNA < 200 copies/mL, defined as the proportion of patients with HIV-1 RNA < 200 copies/mL on their original assigned regimen at week 48 based on Time to Loss of Virological Response (TLOVR) analysis. The tenofovir disoproxil fumarate + emtricitabine + efavirenz group was to be declared non-inferior to the stable baseline regimen (SBR) group if the lower confidence limit of the responder difference (tenofovir disoproxil fumarate + emtricitabine + efavirenz minus SBR) was greater than - 0.15.

Table 5 summarises treatment outcomes through week 48.

Table 5. Outcomes of randomised treatment at week 48 (Study 073)

Outcomes	**Tenofovir/ emtricitabine/ efavirenz**	**Stayed on baseline regimen (SBR)**
HIV-1 RNA < 200 copies/mL (TLOVR)[a]	89% (181/203)	88% (85/97)
HIV-1 RNA < 50 copies/mL	87% (177/203)	85% (82/97)
Median change from baseline in CD4 cell count (cells/mm^3)	+3	+9

The responder difference (HIV-1 RNA <200 copies/mL), tenofovir disoproxil fumarate + emtricitabine + efavirenz minus SBR, was 1% (95% CI: -7% to 9%, p=0.82) at week 48. Tenofovir disoproxil fumarate + emtricitabine + efavirenz was non-inferior to SBR in this study.

There were no differences in HIV symptom index, quality of life and adherence between the tenofovir disoproxil fumarate + emtricitabine + efavirenz and the SBR group. Differences were reported in medication preference; the proportion of patients reporting they preferred tenofovir disoproxil fumarate + emtricitabine + efavirenz compared to their previous regimen increased from 64% at week 4 to 85% at week 48.

5.2 Pharmacokinetic properties

One Tenofovir disoproxil Emtricitabine Efavirenz Mylan tablet is bioequivalent to one tenofovir disoproxil fumarate tablet (300 mg) plus one emtricitabine capsule (200 mg) plus one efavirenz tablet (600 mg) following single-dose administration in fasting healthy subjects (N=45).

The separate pharmaceutical forms of tenofovir disoproxil fumarate, emtricitabine and efavirenz were used to determine the pharmacokinetics of tenofovir disoproxil fumarate, emtricitabine and efavirenz in HIV infected patients.

Tenofovir disoproxil fumarate

The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 6. Following oral administration of tenofovir disoproxil fumarate, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01 to 25 µg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 6. Single dose pharmacokinetic parameters for tenofovir, emtricitabine and efavirenz in adults[1]

	Tenofovir	Emtricitabine	Efavirenz
Fasted oral bioavailability (%)	25	93	N/A
Plasma terminal elimination half-life (hr)	17	10	52 – 72
C_{max} (µg/mL)	0.30 ± 0.09	1.8 ± 0.7[2]	12.9[2,3]
AUC (µg*hr/mL)	2.29 ± 0.69	10.0 ± 3.1[2]	184[2,3]
CL/F (mL/min)	1043 ± 115	302 ± 94	N/A
CL_{renal} (mL/min)	243 ± 33	213 ± 89	N/A

1. Data presented as mean values.
2. Data presented as steady state values.
3. Data on 600 mg dose of efavirenz

N/A Not Available

Emtricitabine

The pharmacokinetic properties of emtricitabine are summarized in Table 6. Following oral administration of emtricitabine 200 mg capsules, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02 to 200 µg/mL. Following administration of radiolabelled emtricitabine approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine 200 mg capsules, the plasma emtricitabine half-life is approximately 10 hours.

Efavirenz

Peak efavirenz plasma concentrations of 1.6 to 9.1 µM were attained by 5 hours following single oral doses of 100 to 1600 mg administered to uninfected volunteers. The steady state mean C_{max}, mean C_{min} and mean AUC were linear with 200 mg, 400 mg and 600 mg daily doses. In 35 patients receiving efavirenz 600 mg once daily, steady state C_{max} was 12.9 µM, steady state C_{min} was 5.6 µM and AUC was 184 µM·h.

Administration of a single 600 mg efavirenz tablet with a high fat/high caloric meal (approximately 1000 kcal, 500 to 600 kcal from fat) was associated with a 28% increase in mean $AUC_{0-\infty}$ of efavirenz and 79% increase in mean C_{max} of efavirenz relative to the exposures achieved when given under fasted conditions.

Efavirenz is highly bound (approximately 99.5 to 99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n=9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3- fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. *In vitro* studies have shown that efavirenz inhibited P450 isozymes 2C9, 2C19 and 3A4 with K_i values (8.5 to 17 µM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82 to 160 µM) only at concentrations well above those achieved clinically.

Efavirenz plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isoenzyme. The clinical implications of such an association are unknown, however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce P450 enzymes resulting in the induction of its own metabolism. Efavirenz has a relatively long terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses. Approximately 14 to 34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

Effect of food on oral absorption

Tenofovir disoproxil Emtricitabine Efavirenz Mylan has not been evaluated in the presence of food. Administration of a single 600 mg efavirenz tablet with a high fat/high caloric meal increased the mean AUC and C_{max} of efavirenz by 28% and 79%, respectively, compared to administration in the fasted state. Compared to fasted administration, dosing of tenofovir disoproxil fumarate and emtricitabine in combination with either a high fat meal or a light meal increased the AUC and C_{max} of tenofovir by approximately 40% and 14%, respectively, without affecting emtricitabine exposures.

Special populations

Children and geriatric patients

Pharmacokinetic studies with Tenofovir disoproxil Emtricitabine Efavirenz Mylan have not been fully evaluated in children (<18 years) or in the elderly (over 65 years) (see section 4.4).

Gender

The pharmacokinetics of tenofovir disoproxil fumarate, emtricitabine and efavirenz are similar in male and female patients.

The pharmacokinetics of tenofovir disoproxil fumarate have not been specifically studied in different ethnic groups.

Renal impairment

Tenofovir disoproxil Emtricitabine Efavirenz Mylan is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50 ml/min)). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet (see section 4.4).

Hepatic impairment

Tenofovir disoproxil Emtricitabine Efavirenz Mylan is not recommended for patients with moderate or severe hepatic impairment because of insufficient data to determine whether dose adjustment of efavirenz is necessary. Patients with mild hepatic impairment may be treated with Tenofovir disoproxil Emtricitabine Efavirenz Mylan. Tenofovir disoproxil Emtricitabine Efavirenz Mylan should be administered with caution to these patients (see section 4.4).

Tenofovir disoproxil fumarate and emtricitabine

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of emtricitabine have not been studied in patients with moderate to severe hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Efavirenz

Because of the extensive cytochrome P450 mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution should be exercised in administering efavirenz to patients with liver disease.

5.3 Preclinical safety data

Animal toxicology

Tenofovir disoproxil fumrate

Tenofovir administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-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 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Carcinogenicity and mutagenicity

No carcinogenicity studies have been conducted with tenofovir disoproxil fumarate, emtricitabine and efavirenz in combination.

Tenofovir disoproxil fumarate

In a long-term carcinogenicity study conducted in mice with tenofovir disoproxil 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 fumarate 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.

Emtricitabine

In long-term oral carcinogenicity studies conducted with emtricitabine, no drug- related increases in tumour incidence were found in mice at doses up to 750 mg/kg/day (32 times the human systemic exposure (AUC) at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (38 times the human systemic exposure at the therapeutic dose).

Emtricitabine was not mutagenic in bacteria or mouse lymphoma cell assays *in vitro* nor clastogenic in the mouse micronucleus test *in vivo*.

Efavirenz

Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75,150 or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumour incidence above background were seen in males. There was no NOAEL in females established for this study because tumour findings occurred at all doses. AUC at the NOAEL (150 mg/kg) in the males was approximately 0.9 times that in humans at the recommended clinical dose. In the rat study no increases in tumour incidence were observed at doses up to 100 mg/kg/day, for which AUCs were 0.1 (males) or 0.2 (females) times those in humans at the recommended clinical dose.

Efavirenz was not genotoxic in assays for gene mutations (*S. typhimurium, E. coli* and Chinese hamster ovary cells) and chromosomal damage (human peripheral blood lymphocytes, Chinese hamster ovary cells, and a mouse micronucleus assay).

Impairment of fertility

Tenofovir disoproxil fumarate

Male and female rat fertility and mating performance or early embryonic development were unaffected by an oral tenofovir disoproxil fumarate dose (600 mg/kg/day) that achieved systemic drug exposures that were in excess of the expected 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.

Emtricitabine

Emtricitabine did not affect fertility in male rats or in female and male mice at respective approximate exposures (AUC) of 130 and 50 to 80 times the exposure in humans. The fertility of offspring was unaffected by treatment of mice from early gestation to the end of lactation (50 times the human exposure).

Efavirenz

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm or offspring of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were below those achieved in humans given therapeutic doses of efavirenz.

6. Pharmaceutical Particulars

6.1 List of excipients

In addition to the active ingredients, the Tenofovir disoproxil Emtricitabine Efavirenz Mylan tablets contain:

- Croscarmellose sodium
- Hyprolose
- Hydroxypropylcellulose
- Magnesium stearate
- Microcrystalline cellulose
- Sodium metabisulfite
- Lactose monohydrate
- Silica colloidal anhydrous
- Iron oxide red
- Opadry pink 85F540043

Tenofovir disoproxil Emtricitabine Efavirenz Mylan is gluten-free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

HDPE bottle with a PP child resistant screw cap and a desiccant. Pack-sizes of 30 film-coated tablets.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

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9. Date of First Approval

26 July 2018

10. Date of Revision of the Text

21 January 2019

Section updated	Summary of changes
4.4	Addition of information regarding QTc prolongation
4.5	Added interaction with ledipasvir / sofosbuvir and sofosbuvir / velpatasvir
5.1	Additional information regarding Cardiac Electrophysiology