Summary of Product Characteristics

Vonaday 600 mg/300 mg/300 mg film coated tablets

1. Name of the medicinal product
Vonaday 600 mg/300 mg/300 mg film-coated tablets

2. Qualitative and quantitative composition
Each film-coated tablet contains 600 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil.

Excipient with known effect

Each film-coated tablet contains (92 mg) of sodium.

For the full list of excipients, see section 6.1

3. Pharmaceutical form
Film-coated tablet.

4. Clinical particulars
4.1 Therapeutic indications
Vonaday is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults.

4.2 Posology and method of administration
Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults

The recommended dose of Vonaday is one tablet taken orally once daily.

It is recommended that Vonaday be taken on an empty stomach since food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions. In order to improve the tolerability to efavirenz with respect to undesirable effects on the nervous system, bedtime dosing is recommended.

If a patient misses a dose of Vonaday within 12 hours of the time it is usually taken, the patient should take Vonaday as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Vonaday by more than 12 hours and it is almost time for the next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Vonaday, another tablet should be taken. If the patient vomits more than 1 hour after taking Vonaday he/she does not need to take another dose.

It is anticipated that tenofovir exposure (AUC) will be approximately 30% lower following administration of Vonaday on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food. Data on the clinical translation of the

decrease in pharmacokinetic exposure are not available. In virologically suppressed patients, the clinical relevance of this reduction can be expected to be limited.

Where discontinuation of therapy with one of the components of Vonaday is indicated or where dose modification is necessary, separate preparations of efavirenz, lamivudine and tenofovir disoproxil fumarate are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If therapy with Vonaday is discontinued, consideration should be given to the long half-life of efavirenz and long intracellular half-life of tenofovir. Because of interpatient variability in these parameters and concerns regarding development of resistance, HIV treatment guidelines should be consulted, also taking into consideration the reason for discontinuation.

Dose adjustment:

If Vonaday is co-administered with rifampicin to patients weighing 50 kg or more, an additional 200 mg/day (800 mg total) of efavirenz may be considered.

Special populations

Elderly people

No data are available on which to make a dose recommendation for patients over the age of 65 years. However, caution should be taken due to decreased hepatic and renal function.

Renal impairment

No dose adjustment of Vonaday is necessary for patients with mild renal impairment whose creatinine clearance more than 50-80mL/min. Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in patients with mild renal impairment. The safety and effectiveness of dose adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment; therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Hepatic impairment

Patients with mild hepatic impairment (Child Pugh A) may be treated with Vonaday without any adjustment in dose. Patients should be monitored carefully for adverse reactions. Vonaday is not recommended in patients with moderate or severe hepatic impairment (Child Pugh B or C).

Paediatric population

Not recommended.

Method of administration

Vonaday tablets should be swallowed whole with water, once daily

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Coadministration of efavirenz, a component of Vonaday with elbasvir and grazoprevir is contraindicated.

4.4 Special warnings and precautions for use

Co-administration with other medicinal products

As a fixed combination, Vonaday should not be administered concomitantly with other medicinal products containing the same active components, lamivudine or tenofovir disoproxil fumarate. Vonaday should not be co-administered with products containing efavirenz unless needed for dose adjustment e.g. with rifampicin (see section 4.2). Due to similarities with lamivudine, Vonaday should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Vonaday should not be administered concomitantly with adefovir dipivoxil or with medicinal products containing tenofovir alafenamide.

Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A. Likewise, efavirenz may alter plasma concentrations of drugs metabolized by CYP3A or CYP2B6. The most prominent effect of efavirenz at steady-state is induction of CYP3A and CYP2B6

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. A majority of these cases have been in women. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues. Treatment with Vonaday 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.

QTc Prolongation

QTc prolongation has been observed with the use of efavirenz. Consider alternatives to Vonaday when coadministered 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

Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behaviour. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continued therapy outweighs the benefits (see section 4.8).

Nervous System Symptoms

Nervous System Symptoms adverse reactions have been reported in patients treated with efavirenz. These symptoms included, but were not limited to, dizziness, insomnia, impaired concentration, somnolence, abnormal dreams, and hallucinations. Dosing at bedtime may improve the tolerability of these nervous system symptoms. Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery. Patients receiving efavirenz should be alerted to the potential for additive central nervous system effects when efavirenz is used concomitantly with alcohol or psychoactive drugs.

Analysis of long-term data showed that, the incidences of new-onset nervous system symptoms among efavirenz -treated patients were generally similar to those in the indinavir-containing control arm.

Embryo-Fetal Toxicity

Efavirenz, a component of Vonaday may cause fetal harm when administered during the first trimester to a pregnant woman. Advise females of reproductive potential who are receiving Vonaday to avoid pregnancy.

Rash

Rash associated with blistering, moist desquamation, or ulceration occurred in patients treated with Efavirenz. The incidence of Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in adult patients treated with Efavirenz. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur with initiating therapy with efavirenz and in most patients continuing therapy with efavirenz.

Vonaday can generally be reinitiated in patients interrupting therapy because of rash. Vonaday should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. For patients who have had a life-threatening cutaneous reaction (eg, Stevens-Johnson syndrome), alternative therapy should be considered.

Exacerbation of Hepatitis after Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including Vonaday, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Vonaday should be closely monitored with both clinical and laboratory follow-ups for at least several months after stopping treatment.

Hepatotoxicity

Vonaday is not recommended for patients with moderate or severe hepatic impairment. Careful monitoring is recommended for patients with mild hepatic impairment receiving Vonaday.

Monitoring of liver enzymes before and during treatment is recommended for all patients. Consider discontinuing Vonaday in patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range.

Discontinue Vonaday if elevation of serum transaminases is accompanied by clinical signs or symptoms of hepatitis or hepatic decompensation

Emergence of Lamivudine-Resistant HBV

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV (see full prescribing information for Lamivudine -HBV). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Lipid Elevations

Treatment with Vonaday has resulted in increases in the concentration of total cholesterol and triglycerides. Cholesterol and triglyceride testing should be performed before initiating Vonaday therapy and at periodic intervals during therapy.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including Vonaday. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, Pneumocystis *jiroveci pneumonia* [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Use with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patient's hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of Vonaday should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening

clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6). See the full prescribing information for interferon and ribavirin.

Convulsions

Convulsions have been observed in adult and pediatric patients receiving efavirenz, generally in the presence of known medical history of seizures. Caution should be taken in any patient with a history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels

New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of Tenofovir.

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with Vonaday. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation and periodically during Vonaday therapy.

No safety or efficacy data are available in patients with renal impairment who received tenofovir DF using these dosing guidelines, so the potential benefit of Vonaday therapy should be assessed against the potential risk of renal toxicity.

Vonaday should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)). Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

Bone effects

Bone Mineral Density:

Tenofovir DF was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving Tenofovir DF.

Clinical trials evaluating Tenofovir DF in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the

Tenofovir DF -treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected.

The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

Mineralization Defects:

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of Tenofovir DF. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF.

Early virologic failure

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

Elderly

The combination of efavirenz, lamivudine or tenofovir has not been studied in patients over the age of 65. Older people are more likely to have decreased hepatic or renal function, therefore caution should be exercised when treating older people with Vonaday.

Excipients

This medicinal product contains sodium, which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed using combination of efavirenz, lamivudine or tenofovir. As Vonaday contains efavirenz, lamivudine and tenofovir disoproxil fumarate,

any interactions that have been identified with these agents individually may occur with Vonaday.

Efavirenz has been shown *in vivo* to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when coadministered with Efavirenz.

Drugs that induce CYP3A activity (e.g, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

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. Consider alternatives to Vonaday when coadministered with a drug with a known risk of Torsade de Pointes.

Drugs Inhibiting Organic Cation Transporters

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Sorbitol

Coadministration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol-containing medicines with Vonaday.

Didanosine

Coadministration of Vonaday and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When administered with Tenofovir DF, C_{max} and AUC of didanosine increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving Tenofovir DF with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with Tenofovir DF. In patients weighing less than 60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with Tenofovir DF. When coadministered, Tenofovir DF and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). For additional

information on coadministration of Tenofovir DF and didanosine, please refer to the full prescribing information for didanosine.

HIV-1 Protease Inhibitors

Tenofovir DF decreases the AUC and Cmin of atazanavir. When coadministered with Tenofovir DF, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Vonaday should not be coadministered with atazanavir without ritonavir.

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations. Tenofovir DF is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir DF is coadministered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving Tenofovir DF concomitantly with lopinavir/ritonavir, ritonavir boosted atazanavir, or ritonavir-boosted darunavir should be monitored for Tenofovir DF-associated adverse reactions. Vonaday should be discontinued in patients who develop Tenofovir DF-associated adverse reactions.

Hepatitis C Antiviral Agents

Coadministration of Tenofovir DF and sofosbuvir/velpatasvir or ledipasvir/sofosbuvir has been shown to increase tenofovir exposure.

In patients receiving Tenofovir DF concomitantly with sofosbuvir/velpatasvir, monitor for adverse reactions associated with tenofovir DF.

In patients receiving Tenofovir DF concomitantly with ledipasvir/sofosbuvir without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, monitor for adverse reactions associated with tenofovir DF.

In patients receiving Tenofovir DF concomitantly with ledipasvir/sofosbuvir and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with tenofovir DF.

Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys, coadministration of Tenofovir DF with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs.

In the treatment of chronic hepatitis B, Vonaday should not be administered in combination with adefovir dipivoxil.

Drug interactions are summarized in Table 1.

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
HIV antiviral agents		
Protease inhibitor: Fosamprenavir Calcium	↓ amprenavir	Fosamprenavir (unboosted): Appropriate doses of the combinations with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir*	*Treatment-naive patients:* When coadministered with efavirenz, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and efavirenz 600 mg (once daily on an empty stomach, preferably at bedtime). *Treatment-experienced patients:* Coadministration of Vonaday and atazanavir is not recommended.
Protease inhibitor: Indinavir	↓ indinavir*	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir*	Lopinavir/ritonavir once daily dosing is not recommended when coadministered with Vonaday. The dose of lopinavir/ritonavir must be increased when coadministered with efavirenz. See the lopinavir/ritonavir prescribing information for dose adjustments of lopinavir/ritonavir when coadministered with efavirenz in adult and pediatric patients.
Protease inhibitor: Ritonavir	↑ ritonavir* ↑ efavirenz*	Monitor for elevation of liver enzymes and for adverse clinical experiences (e.g., dizziness, nausea, paresthesia) when efavirenz is coadministered with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir*	Appropriate doses of the combination of Vonaday and saquinavir/ritonavir with respect to safety and efficacy have not been established.
NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. Vonaday should not be coadministered with other NNRTIs.

CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc*	Refer to the full prescribing information for maraviroc for guidance on coadministration with efavirenz.
Hepatitis C antiviral agents		
Boceprevir	↓Boceprevir	Concomitant administration of boceprevir with efavirenz is not recommended because it may result in loss of therapeutic effect of boceprevir.
Elbasvir/Grazoprevir	↓Elbasvir ↓grazoprevir is	Coadministration of efavirenz with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir.
Pibrentasvir/Glecaprevir	↓ pibrentasvir ↓ glecaprevir	Coadministration of efavirenz is not recommended because it may lead to reduced therapeutic effect of pibrentasvir/glecaprevir.
Simeprevir	↓ simeprevir* ↔ efavirenz*	Concomitant administration of simeprevir with Vonaday is not recommended because it may result in loss of therapeutic effect of simeprevir.
Velpatasvir/ Sofosbuvir	↓ velpatasvir	Coadministration of Vonaday and sofosbuvir/velpatasvir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir
Velpatasvir /Sofosbuvir/ /Voxilaprevir	↓ velpatasvir ↓ voxilaprevir	Coadministration of Vonaday and sofosbuvir/velpatasvir/voxilaprevir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir/voxilaprevir
Other agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin	Monitor INR and adjust warfarin dosage if necessary.
Anticonvulsants: Carbamazepine	↓ carbamazepine* ↓ efavirenz*	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants: Bupropion	↓ bupropion*	Increases in bupropion dosage should be guided by clinical response. Bupropion dose should not exceed the maximum recommended dose.
Sertraline	↓ sertraline*	Increases in sertraline dosage should be guided by clinical response.
Antifungals: Voriconazole	↓ voriconazole* ↑ efavirenz*	Vonaday and voriconazole should not be coadministered at standard doses. When voriconazole is coadministered with Vonaday, voriconazole maintenance dose should be increased to 400 mg every 12 hours and Efavirenz dose should be decreased to 300 mg once daily using the capsule formulation.
Itraconazole	↓itraconazole*	Consider alternative antifungal treatment because

Ketoconazole Posaconazole	↓hydroxyitraconazole * ↓ketoconazole ↓ posaconazole*	no dose recommendation for itraconazole can be made. Consider alternative antifungal treatment because no dose recommendation for ketoconazole can be made. Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ clarithromycin * ↑ 14-OH metabolite*	Consider alternatives to macrolide antibiotics because of the risk of QT interval prolongation
Antimycobacterials: Rifabutin Rifampin	↓ rifabutin* ↓ efavirenz*	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week. Increase Efavirenz to 800 mg once daily when coadministered with rifampin to patients weighing 50 kg or more.
Antimalarials: Artemether/ lumefantrine Atovaquone/ proguanil	↓ artemether* ↓ dihydroartemisinin* ↓ lumefantrine* ↓ atovaquone ↓ proguanil	Consider alternatives to artemether/lumefantrine because of the risk of QT interval prolongation. Concomitant administration is not recommended.
Calcium channel blockers: Diltiazem Others (eg, felodipine, nicardipine, nifedipine, verapamil)	↓diltiazem* ↓ desacetyl diltiazem* ↓ N-monodesmethyl diltiazem* ↓ calcium channel blocker	Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). No dose adjustment of efavirenz is necessary when administered with diltiazem. When coadministered with Vonaday, dosage adjustment of calcium channels blocker may be needed and should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin* ↓ pravastatin* ↓ simvastatin*	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgestimate Implant: Etonogestrel	↓ active metabolites of norgestimate* ↓ etonogestrel	A reliable method of barrier contraception should be used in addition to hormonal contraceptives. A reliable method of barrier contraception should be used in addition to hormonal contraceptives. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in

		efavirenz-exposed patients.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A	↓immunosuppressant	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 efavirenz.
Narcotic analgesic: Methadone	↓ methadone*	Monitor for signs of methadone withdrawal and increase methadone dose if required to alleviate withdrawal symptoms.

* The interaction between Efavirenz and the drug was evaluated in a clinical study. All other drug interactions shown are predicted. This table is not all-inclusive.

4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the new-born, the animal data as well as the clinical experience in pregnant women should be taken into account.

Because of potential teratogenic effects, pregnancy should be avoided in women receiving Vonaday. Females of reproductive potential should undergo pregnancy testing before initiation of Vonaday.

Efavirenz: There are retrospective postmarketing reports of findings consistent with neural tube defects, including meningomyelocele, all in infants of mothers exposed to efavirenz-containing regimens in the first trimester. Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of approximately 1000 live births following exposure to efavirenz-containing regimens (including over 800 live births exposed in the first trimester), there was no difference between efavirenz and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program. As of the interim APR report issued December 2014, the prevalence of birth defects following first-trimester exposure was 2.3% (95% CI: 1.4%-3.6%). One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported. This case also included severe oblique facial clefts and amniotic banding, which have a known association with anophthalmia.

Tenofovir disoproxil fumarate: There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, tenofovir DF should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

Lamivudine: Based on prospective reports from the Antiretroviral Pregnancy Registry of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,300 exposed in the first trimester), there was no difference between lamivudine and overall birth defects compared with the background birth defect rate of 2.7% in the US reference population of the MACDP. The prevalence of defects in the first trimester was 3.1% (95% CI: 2.6% to 3.7%).

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

Breast-feeding

Efavirenz, lamivudine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of efavirenz, lamivudine and tenofovir in new-borns/infants. A risk to the infants cannot be excluded. Therefore, the combination of efavirenz, lamivudine and tenofovir disoproxil fumarate should not be used during breast-feeding.

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

Contraception

Females of reproductive potential should use effective contraception during treatment with efavirenz and for 12 weeks after discontinuing efavirenz due to the long half-life of efavirenz. Barrier contraception should always be used in combination with other methods of contraception. Hormonal methods that contain progesterone may have decreased effectiveness.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, dizziness has been reported during treatment with efavirenz and tenofovir disoproxil fumarate. Efavirenz may also cause impaired concentration and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000), Not known (frequency cannot be estimated from the available data)

System organ class	**Frequency**	**Adverse drug reactions**
Blood and lymphatic system disorders	Not Known	Anemia (including pure red cell aplasia and severe anemias progressing on therapy, lymphadenopathy,
Immune system disorders	Not Known	Anaphylaxis, urticaria, allergic reactions,
Endocrine disorders	Not Known	Hyperglycemia
Metabolism and nutrition disorders	Very common	Hypophosphatemia
	Uncommon	Hypokalemia
	Rare	Lactic acidosis
	Not Known	Lipodystrophy, weight loss, redistribution/accumulation of body fat, malabsorption, hypercholesterolemia, hypertriglyceridemia
Psychiatric disorders	Common	Depression, anxiety, abnormal dreams
	Uncommon	Confusional state, mania, psychosis
	Rare	Neurosis, suicide,
		Nervousness, hallucinations, stupor, abnormal thinking, depersonalization, impaired concentration, aggressive reactions, delusions, emotional lability, catatonia

System organ class	Frequency	Adverse drug reactions
Nervous system disorders	Very common	Dizziness
	Common	Headache, insomnia, somnolence, cerebellar coordination and balance disturbances, convulsions
	Uncommon	Euphoria, agitation, amnesia, ataxia, tremor, abnormal coordination, hypoesthesia, paraesthesia, neuropathy
	Rare	Peripheral neuropathy
Ear and labyrinth disorders	Uncommon	Vertigo, tinnitus
	Not Known	Signs or symptoms of ears
Cardiac disorders	Not known	palpitations
Vascular disorders	Uncommon	flushing
Respiratory, thoracic and mediastinal disorders	Common	Cough
	Not known	Pneumonia, sinusitis, upper respiratory tract infections, dyspnea, abnormal breath sounds/wheezing, nasal discharge or congestion
Gastrointestinal disorders	Very common	Nausea, vomiting
	Common	Abdominal pain, flatulence
	Uncommon	Pancreatitis
	Rare	Increased amylase
	Not known	Diarrhea, dyspepsia, anorexia, abdominal cramps, stomatitis, splenomegaly, constipation
Hepatobiliary disorders	Uncommon	Increased liver enzymes (most commonly AST, ALT gamma GT), hepatitis
	Rare	Hepatic steatosis, hepatic failure,
	Not known	Hepatomegaly, post-treatment exacerbations of hepatitis b,
Skin and subcutaneous	Very common	Rash events

System organ class	Frequency	Adverse drug reactions
tissue disorders:	Common	Alopecia, pruritus,
	Uncommon	Erythema multiforme, Stevens-Johnson syndrome
	Rare	Angioedema, photoallergic dermatitis
	Not known	Sweating, urticaria,
Musculoskeletal and connective tissue disorders:	Common	Arthralgia
	Uncommon	Rhabdomyolysis, muscular weakness
	Rare	Osteomalacia (manifested as bone pain and which may contribute to fractures), myopathy
	Not known	Myalgia, muscle weakness,
Renal and urinary disorders	Uncommon	Increased creatinine
	Rare	Acute renal failure, renal failure, acute tubular necrosis, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus,
	Not known	Renal insufficiency, proteinuria, polyuria, CPK elevation,
Reproductive system and breast disorders	Not known	Gynecomastia
General disorders and administration site conditions:	Very common	Asthenia
	Common	Fever, fatigue,
	Uncommon	Weakness
	Not known	Back pain, chills,

4.9 Overdose

Efavirenz

Some patients accidentally taking 600 mg of efavirenz twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions. Treatment of overdose with Efavirenz 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 drug. There is no specific antidote for overdose with Efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

Lamivudine

There is no known specific treatment for overdose with lamivudine. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Limited clinical experience at doses higher than the therapeutic dose of tenofovir DF 300 mg is available. tenofovir DF 600 mg was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

Tenofovir DF

If overdose occurs the patient must be monitored for evidence of toxicity and standard supportive treatment applied as necessary. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir DF, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, antivirals for treatment of HIV infections, combinations, ATC code: J05AR11

Mechanism of action and pharmacodynamic effects

Efavirenz:

Mechanism of Action

Efavirenz is an NNRTI of HIV-1. Efavirenz activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase. HIV-2 reverse transcriptase and human cellular DNA polymerases α, β, γ, and δ are not inhibited by efavirenz.

Antiviral Activity in Cell Culture

The concentration of efavirenz inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90-95% (EC_{90-95}) ranged from 1.7 to 25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/monocyte cultures. Efavirenz demonstrated antiviral activity against clade B and most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses. Efavirenz demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine and

nevirapine, NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. Efavirenz demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. Efavirenz was not antagonistic with adefovir, used for the treatment of hepatitis B virus infection, or ribavirin, used in combination with interferon for the treatment of hepatitis C virus infection.

Resistance

In cell culture

In cell culture, HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in EC90 value) emerged rapidly in the presence of drug. Genotypic characterization of these viruses identified single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in reverse transcriptase.

Cross-Resistance

Cross-resistance among NNRTIs has been observed. Clinical isolates previously characterized as efavirenz-resistant were also phenotypically resistant in cell culture to delavirdine and nevirapine compared to baseline. Delavirdine-and/or nevirapine-resistant clinical viral isolates with NNRTI resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A, Y181X, Y188X, G190X, P225H, F227L, or M230L) showed reduced susceptibility to efavirenz in cell culture. Greater than 90% of NRTI-resistant clinical isolates tested in cell culture retained susceptibility to efavirenz.

Lamivudine:

Mechanism of Action

Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

Antiviral Activity

The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and fresh human peripheral blood lymphocytes (PBMCs) using standard susceptibility assays. EC50 values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC50 values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC50 values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. Lamivudine was not antagonistic to all tested anti-HIV agents. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Resistance

Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either valine or isoleucine (M184V/I).

Cross-Resistance

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). Lamivudine-resistant HIV-1 mutants were cross-resistant in cell culture to didanosine (ddI). Cross-resistance is also expected with abacavir and emtricitabine as these select M184V substitutions.

Tenofovir disoproxil fumarate

Mechanism of Action

Tenofovir DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ.

Activity against HIV

Antiviral Activity

The 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 EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 μM to 8.5 μM. In drug combination studies, tenofovir was not antagonistic with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir). Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 μM to 2.2 μM) and strain-specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM).

Resistance

HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2to 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 tenofovir.

Cross Resistance

Cross resistance among certain reverse transcriptase inhibitors has been recognized. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with this substitution also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross resistance among these drugs may occur in patients whose virus harbors the K65R or K70E substitution. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of three zidovudine-associated reverse transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir.

5.2 Pharmacokinetic properties

Absorption

Efavirenz

Peak efavirenz plasma concentrations of 1.6-9.1 μM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in Cmax and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. In HIV-1-infected patients at steady state, mean C_{max}, mean Cmin, and mean AUC were dose proportional following 200 mg, 400 mg, and 600 mg daily doses. Time-to-peak plasma concentrations were approximately 3-5 hours and steady-state plasma concentrations were reached in 6-10 days. In 35 patients receiving efavirenz 600 mg once daily, steady-state Cmax was 12.9 ± 3.7 μM (mean ± SD), steady-state Cmin was 5.6 ± 3.2 μM, and AUC was 184 ± 73 μM•h.

Lamivudine

The steady-state pharmacokinetic properties of the lamivudine 300-mg tablet once daily for 7 days compared with the lamivudine 150-mg tablet twice daily for 7 days were assessed in a crossover trial in 60 healthy subjects. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. Absolute bioavailability in 12 adult subjects was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution. After oral administration of 2 mg per kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration (Cmax) was 1.5 ± 0.5 mcg per mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and Cmax increased in proportion to oral dose over the range from 0.25 to 10 mg per kg. The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg per kg twice daily.

Tenofovir DF

Tenofovir DF is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from Tenofovir DF in fasted subjects is approximately 25%. Following oral administration of a single dose of Tenofovir DF 300mg to HIV-1 infected subjects in the fasted state, maximum serum concentrations (Cmax) are achieved in 1.0 ± 0.4 hrs. Cmax and AUC values are 0.30 ± 0.09 □g/mL and 2.29 ± 0.69 □g•hr/mL, respectively.

The pharmacokinetics of tenofovir are dose proportional over a Tenofovir DF dose range of 75 to 600 mg and are not affected by repeated dosing.

Effect of food

Efavirenz

Administration of a single 600 mg efavirenz tablet with a high-fat/high-caloric meal (approximately 1000 kcal, 500-600 kcal from fat) was associated with a 28% increase in mean AUC∞ of efavirenz and a 79% increase in mean Cmax of efavirenz relative to the exposures achieved under fasted conditions.

Lamivudine

Lamivudine tablets and oral solution may be administered with or without food. An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-1-infected subjects on 2 occasions, once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (Tmax: 3.2 ± 1.3 hours) compared with the fasted state (Tmax: 0.9 ± 0.3 hours); Cmax in the fed state was 40% ± 23% (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC∞) in the fed and fasted states.

Tenofovir DF

Administration of Tenofovir DF 300 mg tablets following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in Cmax of approximately 14%. However, administration of Tenofovir DF with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir Cmax by approximately 1 hour. C_{max} and AUC of tenofovir are 0.33 ± 0.12 μg/mL and 3.32 ± 1.37 μg•hr/mL following multiple doses of Tenofovir DF 300 mg once daily in the fed state, when meal content was not controlled.

Distribution

Efavirenz

Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients 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.

Lamivudine

The apparent volume of distribution after IV administration of lamivudine to 20 subjects was 1.3 ± 0.4 L per kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. Binding of lamivudine to human plasma proteins is less than 36%. In vitro studies showed that over the concentration range of 0.1 to 100 mcg per mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 □g/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Biotransformation

Efavirenz

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolized 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 CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP enzymes, resulting in the induction of its own metabolism. Multiple doses of 200-400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22-42% lower) and a shorter terminal half-life of 40-55 hours (single dose half-life 52-76 hours).

Lamivudine

Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). Serum concentrations of this metabolite have not been determined. Lamivudine is not significantly metabolized by cytochrome P450 enzymes.

Tenofovir DF

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.

Following IV administration of tenofovir, approximately 70−80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of Tenofovir DF, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of Tenofovir DF 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.

Elimination

Efavirenz

Efavirenz has a terminal half-life of 52-76 hours after single doses and 40-55 hours after multiple doses. A one-month mass balance/excretion study was conducted using 400 mg per day with a ^{14}C-labeled dose administered on Day 8. Approximately 14-34% of the radiolabel was recovered in the urine and 16-61% was recovered in the feces. Nearly all of the urinary excretion of the radiolabeled drug was in the form of metabolites. Efavirenz accounted for the majority of the total radioactivity measured in feces.

Lamivudine

The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL per min (mean ± SD). In 20 HIV-1-infected subjects given a single IV dose, renal clearance was 280.4 ± 75.2 mL per min (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine. In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life (t½) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0.25 to 10 mg per kg.

Tenofovir DF

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

Gender and race

Efavirenz

The pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied.

Tenofovir DF

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Tenofovir pharmacokinetics are similar in male and female subjects.

Renal impairment

Efavirenz

The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

Lamivudine

The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function.

Pharmacokinetic Parameters (Mean ± SD) after a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults with Varying Degrees of Renal Function

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	>60 mL/min (n = 6)	10-30 mL/min (n = 4)	<10 mL/min (n = 6)
Creatinine clearance (mL/min) Cmax (mcg/mL) AUC∞ (mcg•h/mL) Cl/F (mL/min)	111 ± 14 2.6 ± 0.5 11.0 ± 1.7 464 ± 76	28 ± 8 3.6 ± 0.8 48.0 ± 19 114 ± 34	6 ± 2 5.8 ± 1.2 157 ± 74 36 ± 11

Tmax was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment.

Tenofovir DF

The pharmacokinetics of tenofovir are altered in subjects with renal impairment. In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, Cmax, and AUC of tenofovir were increased. It is recommended that the dosing interval for Tenofovir DF be modified in patients with estimated creatinine clearance below 50 mL/min or in patients with ESRD who require dialysis.

Hepatic impairment

Efavirenz

A multiple-dose study showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh Class B or C) affects efavirenz pharmacokinetics.

Lamivudine

The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Tenofovir DF

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

5.3 Preclinical safety data
***Efavirenz*:**

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 tumor incidence above background were seen in males. There was no NOAEL in females established for this study because tumor 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 tumor 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.

Mutagenesis

Efavirenz tested negative in a battery of in vitro and in vivo genotoxicity assays. These included bacterial mutation assays in S. typhimurium and E. coli, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an in vivo mouse bone marrow micronucleus assay.

Impairment of Fertility

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. The AUCs at the NOAEL values in male (200 mg/kg) and female (100 mg/kg) rats were approximately ≤0.15 times that in humans at the recommended clinical dose.

Animal Toxicology

Non-sustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4-to 13-fold greater than those in humans given the recommended dose.

Lamivudine:

Carcinogenesis

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg.

Mutagenesis

Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver. Lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2,000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

Impairment of Fertility

In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg per kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

***Tenofovir disoproxil fumarate*:**

Carcinogenesis

Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Mutagenesis

Tenofovir DF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir DF was negative when administered to male mice.

Impairment of Fertility

There were no effects on fertility, mating performance or early embryonic development when tenofovir DF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose
Croscarmellose Sodium
Sodium Lauryl Sulphate
Hydroxypropyl cellulose
Colloidal Silicon Dioxide

Sodium Chloride
Magnesium Stearate
Hypromellose
Polysorbate 80
Purified Water
Opadry II White 85F18422

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Proposed 2 years

6.4 Special precautions for storage
Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) {See USP Controlled Room Temperature}.

6.5 Nature and contents of container
30 tablets are packed in HDPE bottle container.

90 tablets are packed in HDPE bottle container

6.6 Special precautions for disposal and other handling
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after {EXP}. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

7. Marketing authorisation holder
Emcure Pharmaceuticals Limited.

8. Marketing authorisation number(s)
To be assigned

9. Date of first authorisation/renewal of the authorisation
Not Applicable

10. Date of revision of the text
Not Applicable.