1. NAME OF THE MEDICINAL PRODUCT

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600 mg/ 300 mg/300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of Efavirenz USP, 300 mg of Lamivudine USP and 300 mg of Tenofovir Disoproxil Fumarate equivalent to 245 mg of Tenofovir Disoproxil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

Description: Yellow colored, capsule shaped, bevel edged biconvex film coated tablets debossed with 'I' on one side and '127' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets are indicated for use alone as a complete regimen or in combination with other antiretrovirals for the treatment of human immunodeficiency virus (HIV-1) infection.

4.2 Posology and method of administration

Adults and Adolescents > 16 years of age

The recommended oral dose of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in HIV-1 Infected adults and adolescents > 16 years of age is 600mg/300 mg/300 mg once daily. It is recommended that efavirenz, lamivudine and tenofovir disoproxil fumarate tablets be taken on an empty stomach, preferably at bed time. If efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are administered to a patient infected with HIV-1 and HBV, the dosage indicated for HIV-1 therapy should be used as part of an appropriate combination regimen. The increased Efavirenz concentrations observed following administration of efavirenz, lamivudine and tenofovir Disoproxil fumarate tablets with may lead to an increase in frequency of adverse reaction. Dosing at bedtime may improve the tolerability of nervous system symptoms.

Pediatric Patients

The recommended oral dose of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in HIV-1 Infected pediatric patients is 600mg/300 mg/300 mg once daily.

Patients with Renal Impairment

Dosing of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is adjusted in accordance with renal impairment.

4.3 Contraindications

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets are contraindicated in patients with previously demonstrated, clinically significant hypersensitivity to any of the components contained in the formulation. See below Table for drug interactions

Table: Drugs that are Contraindicated or Not Recommended for Use with Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Drug Class: Drug Name	Clinical Comment
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine,	Potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Benzodiazepines: midazolam, triazolam	Potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias
St. John's wort *(Hypericum perforatum)*	May lead to loss of virologic response and possible resistance to efavirenz or to the class of nonnucleoside reverse transcriptase inhibitors (NNRTI).

4.4 Special warnings and precautions for use

Efavirenz

Drug Interactions

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.

Resistance

Efavirenz must not be used as a single agent to treat HIV-1 infection or added on as a sole agent to a failing regimen. Resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance.

Co administration with Related Products

Coadministration of efavirenz with ATRIPLA (efavirenz 600mg/emtricitabine 200 mg /tenofovir disoproxil fumarate300 mg) is not recommended, since efavirenz is one of its active ingredients.

Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1008 patients treated with regimens containing efavirenz for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study 006, treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control-treated patients. One percent of efavirenz-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits.

Nervous System Symptoms

Fifty-three percent (531/1008) of patients receiving efavirenz in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (28.1% of the 1008 patients), insomnia (16.3%), impaired concentration (8.3%), somnolence
(7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in 2.0% of patients and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. 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. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms. Dosing at bedtime may improve the tolerability of these nervous system symptoms.

Analysis of long-term data from Study 006 (median follow-up 180 weeks, 102 weeks, and 76 weeks for patients treated with efavirenz + zidovudine + lamivudine, efavirenz + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the indinavir-containing control arm.

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.

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.

Reproductive Risk Potential

Pregnancy Category D. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving efavirenz. Barrier contraception must always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

There are no adequate and well-controlled studies in pregnant women. Efavirenz should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options.

Rash

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with efavirenz. The incidence of Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in patients treated with efavirenz in all studies and expanded access was 0.1%. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16days). The discontinuation rate for rash in clinical trials was 1.7% (17/1008). Efavirenz can be reinitiated in patients interrupting therapy because of rash. Efavirenz 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.

Rash was reported in 26 of 57 pediatric patients (46%) treated with efavirenz capsules. One pediatric patient experienced Grade 3 rash (confluent rash with fever), and two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 8 days. Prophylaxis with appropriate antihistamines before initiating therapy with efavirenz in pediatric patients should be considered.

Hepatotoxicity

Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity. A few of the postmarketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors. 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 efavirenz needs to be weighed against the unknown risks of significant liver toxicity.

Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Caution must 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.

Lipid Elevations

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

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including efavirenz. 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.

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.

Lamivudine

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. 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 lamivudine to any patient with known risk factors for liver disease; however, cases also have been reported in patients with no known risk factors. Treatment with lamivudine 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).

Patients with HIV-1 and Hepatitis B Virus Co-infection

Post-treatment Exacerbations of Hepatitis: In clinical trials in non-HIV-1- infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of post-treatment exacerbations of hepatitis.

Important Differences Among Lamivudine-Containing Products: Lamivudine Tablets contain a higher dose of the same active ingredient (lamivudine) than EPIVIR- HBV Tablets. EPIVIRHBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV. If treatment with EPIVIR-HBV is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the sub-therapeutic dose and the inappropriateness of monotherapy HIV-1 treatment. If a decision is made to administer lamivudine to patients co-infected with HIV-1 and HBV, lamivudine tablets, COMBIVIR® (lamivudine/zidovudine) Tablets, EPZICOM® (abacavir sulfate and lamivudine) Tablets, or TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) Tablets should be used as part of an appropriate combination regimen. Emergence of Lamivudine-Resistant HBV: In non-HIV-l-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response. Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who h a v e received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Use with Other Lamivudine- and Emtricitabine-Containing Products

Lamivudine should not be administered concomitantly with other lamivudine- containing products including EPIVIR-HBV Tablets, COMBIVIR (Lamivudine/zidovudine) Tablets, EPZICOM (abacavir sulfate and lamivudine) Tablets, or TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine) or emtricitabine-containing products, including ATRIPLA® (efavirenz, emtricitabine, and tenofovir), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine and tenofovir), or COMPLERA™ (rilpivirine/emtricitabine/tenofovir).

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-l/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-l/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-l/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 lamivudine 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 >6). See the complete prescribing information for interferon and ribavirin.

Pancreatitis

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretrovira1 therapy, including lamivudine. 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 jirovecii 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.

Tenofovir disoproxil fumarate

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, in combination with other antiretrovirals. 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 analogs 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 Disoproxil fumarate 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).

Exacerbation of Hepatitis after Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including tenofovir disoproxil fumarate, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Tenofovir disoproxil fumarate should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

New Onset or Worsening Renal Impairment

Tenofovir is principally eliminated by the kidney. 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 disoproxil fumarate.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate. Routine monitoring of calculated

creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA®.

Dosing interval adjustment of tenofovir disoproxil fumarate and close monitoring of renal function are recommended in all patients with creatinine clearance below 50 ml/min. No safety or efficacy data are available in patients with renal impairment who received tenofovir disoproxil fumarate using these dosing guidelines, so the potential benefit of tenofovir disoproxil fumarate therapy should be assessed against the potential risk of renal toxicity. Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent.

Coadministration with Other Products

Tenofovir disoproxil fumarate should not be used in combination with the fixed-dose combination products ATRIPLA, COMPLERA, or TRUVADA since tenofovir disoproxil fumarate is a component of these products.

Tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (adefovir dipivoxil).

Patients Coinfected with HIV-1 and HBV

Due to the risk of development of HIV-1 resistance, tenofovir disoproxil fumarate should only be used in HIV-1and HBV coinfected patients as part of an appropriate antiretroviral combination regimen.

HIV-1 antibody testing should be offered to all HBV- infected patients before initiating therapy with tenofovir disoproxil fumarate. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment wit tenofovir disoproxil fumarate.

Decreases in Bone Mineral Density

Assessment of bone mineral density (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.

In HIV-1 infected adult subjects treated with tenofovir disoproxil fumarate in study 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the trial. At week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (- 1.0% ± 4.6). Changes in BMD at

the hip were similar between the two treatment groups (-2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the trial and this reduction was sustained through week 144. Twenty-eight percent of tenofovir Disoproxil fumarate-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary Ntelopeptide) in the tenofovir disoproxil fumarate group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1, 25 vitamin D levels were also higher in the tenofovir disoproxil fumarate group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range.

In clinical trials evaluating tenofovir disoproxil fumarate in HIV-1 infected pediatric subjects 2 to less than 18 years of age, bone effects were similar to those observed in adult subjects. Under normal circumstances BMD increases rapidly in pediatric patients. In study 352 (2 to less than 12 years), the mean rate of BMD gain in lumbar spine at week 48 was similar between the Tenofovir disoproxil fumarate and the d4T or AZT treatment groups. Total body BMD gain was less in the tenofovir disoproxil fumarate compared to the d4T or AZT treatment group. One Tenofovir disoproxil fumarate-treated subject and none of the d4T or AZT- treated subjects experienced significant (greater than 4%) lumbar spine BMD loss at week 48. Changes from baseline in BMD Z-scores were -0.012 for lumbar spine and -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In study 321 (12 to less than 18 years), the mean rate of BMD gain at week 48 was less in the tenofovir disoproxil fumarate compared to the placebo treatment group. Six tenofovir disoproxil fumarate treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at week 48. Changes from baseline BMD Z-scores were -0.341 for lumbar spine and -0.458 for total body in the 28 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In both trials, skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil fumarate-treated pediatric subjects suggest increased bone turnover, consistent with the effects observed in adults.

The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Cases of osteomalacia (associated with

proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir disoproxil fumarate. The bone effects of tenofovir disoproxil fumarate have not been studied in patients with chronic HBV infection.

Fat Redistribution

In HIV-infected patients 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 combination
antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including tenofovir disoproxil fumarate. 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 jirovecii 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz

Drug-Drug Interactions

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 co administered with efavirenz. In vitro studies have demonstrated that efavirenz inhibits CYP2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Co-administration of Efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the co-administered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs that induce CYP3A activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with efavirenz are summarized in below table. The tables include potentially significant interactions, but are not all inclusive.

Table: 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**
Antiretroviral 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 i.e.administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when efavirenz i.e. administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir	*Treatment-naïve 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:* Co-administration of efavirenz 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. When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily), the indinavir AUC and Cmin were decreased on average by 33 to 46% and 39 to 57%, respectively, compared to when indinavir (800 mg every 8 hours) was given alone.

Concomitant Drug Class: Drug Name	EFFECT	Clinical Comment
Protease inhibitor: Lopinavir/ritonavir	↓LOPINAVIRA	Lopinavir/ritonavir tablets should not be administered once daily in combination with efavirenz. In antiretroviral-naïve patients, lopinavir/ritonavir tablets can be used twice daily in combination with efavirenz with no dose adjustment. A dose increase of lopinavir/ritonavir tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). A dose increase of lopinavir/ritonavir oral solution to 533/133 mg (6.5 mL) twice daily taken with food is recommended when used in combination with efavirenz.

Protease inhibitor: Ritonavir	↑RITONAVIRA ↓EFAVIRENZA	When ritonavir 500 mg q12h was coadministered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓SAQUINAVIRA	Should not be used as sole protease inhibitor in combination with efavirenz.
CCR5 co-receptor antagonist: Maraviroc	↓MARAVIROCA	Refer to the full prescribing information for maraviroc for guidance on Coadministration with efavirenz.
Other agents		
Anticoagulant: Warfarin	↑OR ↓ WARFARIN	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓CARBAMAZEPINEA ↓EFAVIREdNZA	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 Sertraline	↓BYTIPOIIONA ↓ ↓SERTRALINEA	The effect of efavirenz on bupropion exposure is thought to be due to the induction of bupropion metabolism. Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. Increases in sertraline dosage should be guided by clinical response.
Antifungals: Voriconazole	↓voriconazole ↑ efavirenz[a]	Efavirenz and voriconazole must not be coadministered at standard doses. Efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases

		efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects. When voriconazole is coadministered with efavirenz, 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. Efavirenz tablets should not be broken.
Itraconazole	↓itraconazole ↓	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered
Ketoconazole	↓ ketoconazole	Drug interaction studies with efavirenz and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Posaconazole	↓ posaconazole	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓clarithromycin ↑ 14-OH metabolite	Plasma concentrations decreased by efavirenz; clinical significance unknown. 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, such as azithromycin, should be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.
Antimycobacterial: Rifabutin	↓rifabutin	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	↓efavirenz	If efavirenz is coadministered with rifampin to patients weighing 50 kg or more, an increase in the dose of efavirenz to 800 mg once daily is recommended.
Calcium channel blockers: Diltiazem	↓diltiazem ↓ desacetyl diltiazem ↓N-monodesmethyl diltiazem[a]	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.

Others (eg, felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).
Hormonal contraceptives: Oral Ethinyl Norgestimate Implant Etonogestrel	estradiol/ ↓ active metabolites of norgestimate ↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/ norgestimate on efavirenz plasma concentrations was observed. A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. 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	Decreased exposure of the immunosuppressant may be expected due to CYP3A induction. These immunosuppressants are not anticipated to affect exposure of efavirenz. 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	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal.

		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.

Other Drugs

Based on the results of drug interaction studies no dosage adjustment is recommended when efavirenz is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, Tenofovir disoproxil fumarate, and zidovudine.

Specific drug interaction studies have not been performed with efavirenz and NRTIs other than lamivudine and zidovudine. Clinically significant interactions would not be expected since the NRTIs are metabolized via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Cannabinoid Test Interaction

Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving efavirenz when the Microgenics CEDIA DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry.

Of the three assays analyzed (Microgenics CEDIA DAU Multi-Level THC assay, Cannabinoid Enzyme Immunoassay [Diagnostic Reagents, Inc], and AxSYM Cannabinoid Assay), only the Microgenics CEDIA DAU Multi-Level THC assay showed false-positive results. The other two assays provided true-negative results. The effects of efavirenz on cannabinoid screening tests other than these three are unknown. The manufacturers of cannabinoid assays should be contacted for additional information regarding the use of their assays with patients receiving efavirenz.

LAMIVUDINE

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.

Interferon- And Ribavirin-Based Regimens

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-l/hcv co-infected patients, hepatic decompensation (some fatal) Has occurred in hiv–l/hcv co-infected patients receiving combination antiretroviral Therapy for hiv-1 and interferon alfa with or without ribavirin.

Zalcitabine

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another.therefore, use of lamivudine in combination with zalcitabine is not recommended.

Trimethoprim/sulfamethoxazole (tmp/smx)

No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of tmp/smx such as those used to treat PCP.

Drugs with no observed interactions with lamivudine

A drug interaction study showed no clinically significant interaction between lamivudine and zidovudine

Tenofovir disoproxil fumarate

This section describes clinically relevant drug interactions with tenofovir disoproxil fumarate.

Drug interactions trials are described elsewhere in the labeling.

Didanosine

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

When administered with tenofovir disoproxil fumarate, cmax and auc of didanosine (administered as either the buffered or enteric-coated formulation) 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 disoproxil fumarate (tenofovir df) with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with tenofovir disoproxil fumarate. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered,

tenofovir disoproxil fumarate and didanosine ec may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with tenofovir disoproxil fumarate should be under fasted conditions.

Atazanavir

Atazanavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and tenofovir disoproxil fumarate should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

Tenofovir disoproxil fumarate decreases the auc and cmin of atazanavir. When coadministered withtenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with tenofovir Disoproxil fumarate.

Lopinavir/ritonavir

Lopinavir/ritonavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and tenofovir disoproxil fumarate should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir disoproxil fumarateassociated adverse reactions.

Drugs affecting renal function

Since tenofovir is primarily eliminated by the kidneys, coadministration of tenofovir disoproxil fumarate 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, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir. In the treatment of chronic hepatitis b, tenofovir disoproxil fumarate should not be administered in combination with hepsera (adefovir dipivoxil).

4.6 Pregnancy and lactation

Efavirenz

Pregnancy: Teratogenic Effects:

Pregnancy Category D: Please refer warnings and precautions

Antiretroviral Pregnancy Registry:

As of July 2010, the Antiretroviral Pregnancy Registry has received prospective reports of 792 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (718 pregnancies). Birth defects occurred in 17 of 604 live births (first-trimester exposure) and 2 of 69 live births (second/third-trimester exposure). 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; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. There have been six retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of Efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

Animal Data

Effects of efavirenz on embryo-fetal development have been studied in three nonclinical species (cynomolgus monkeys, rats, and rabbits). In monkeys, efavirenz 60 mg/kg/day was administered to pregnant females throughout pregnancy (gestation days 20 through 150). The maternal systemic drug exposures (AUC) were 1.3 times the exposure in humans at the recommended clinical dose (600 mg/day), with fetal umbilical venous drug concentrations approximately 0.7 times the maternal values. Three fetuses of 20 fetuses/infants had one or more malformations; there were no malformed fetuses or infants from placebo-treated mothers. The malformations that occurred inthese three monkey fetuses included anencephaly and unilateral anophthalmia in one fetus, microophthalmia in a second, and cleft palate in the third. There was no NOAEL (no observable adverse effect level) established for this study because only one dosage was evaluated. In rats, efavirenz was administered either during organogenesis (gestation days 7 to 18) or from gestation day 7 through lactation day 21 at 50, 100, or 200 mg/kg/day. Administration of 200 mg/kg/day in rats was associated with increase in the incidence of early resorptions; and doses 100 mg/kg/day and greater were associated with early neonatal mortality. The AUC at the NOAEL (50 mg/kg/day) in this rat study was 0.1 times that in humans at the recommended clinical dose. Drug concentrations in the milk on lactation day 10 were approximately 8 times higher than those in maternal plasma. In pregnant rabbits, efavirenz was neither embryo lethal nor teratogenic when administered at doses of 25, 50, and 75 mg/kg/day over the period of organogenesis (gestation days 6

through 18). The AUC at the NOAEL (75 mg/kg/day) in rabbits was 0.4 times that in humans at the recommended clinical dose.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats. Because of the potential for HIV transmission and the potential for serious adverse effects in nursing infants, mothers should be instructed not to breast-feed if they are receiving efavirenz.

Pediatric Use

ACTG 382 is an ongoing, open-label study in 57 NRTI-experienced pediatric patients to characterize the safety, pharmacokinetics, and antiviral activity of efavirenz in combination with
nelfinavir (20 to 30 mg/kg three times daily) and NRTIs. Mean age was 8 years (range 3 to 16).
Efavirenz has not been studied in pediatric patients below 3 years of age or who weigh less than 13 kg. At 48 weeks, the type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of rash, which was reported in 46% (26/57) of pediatric patients compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric patients compared to 0.9% of adults.

The starting dose of efavirenz was 600 mg once daily adjusted to body size, based on weight, targeting AUC levels in the range of 190 to 380 μM•h. The pharmacokinetics of efavirenz in pediatric patients were similar to the pharmacokinetics in adults who received 600-mg daily doses of efavirenz. In 48 pediatric patients receiving the equivalent of a 600-mg dose of efavirenz, steady-state Cmax was 14.2 ± 5.8 μM (mean ± SD), steady-state Cmin was 5.6 ± 4.1 μM, and AUC was 218 ± 104 μM•h.

Geriatric Use

Clinical studies of efavirenz did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

Hepatic Impairment

Efavirenz is not recommended for patients with moderate or severe hepatic impairment because
there are insufficient data to determine whether dose adjustment is necessary. Patients with mild

hepatic impairment may be treated with efavirenz without any adjustment in dose. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering efavirenz to these patients.

Lamivudine

Pregnancy: Teratogenic Effects:

Pregnancy Category C. There are no adequate and well- controlled studies of lamivudine in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of teratogenicity. Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans. Lamivudine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies conducted in South Africa. The study 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 studies 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, lamivudine amniotic fluid specimens were collected following natural rupture of membranes. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily). It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1- infected patients.

Animal reproduction studies performed at oral doses up to 130 and 60 times the adult dose in rats and rabbits, respectively, revealed no evidence of teratogenicity due to lamivudine. Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans. However, there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Based on animal studies, lamivudine crosses the placenta and is transferred to the fetus.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-l infection. Because of

the potential for serious adverse reactions in nursing infants and HIV-l transmission, mothers should be instructed not to breastfeed if they are receiving lamivudine.

Lamivudine is excreted into human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Pediatric Use

The safety and effectiveness of twice-daily lamivudine in combination with other antiretroviral agents have been established in pediatric patients 3 months and older.

Geriatric Use

Clinical studies of lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, because lamivudine is substantially excreted by the kidney and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly.

Patients with Impaired Renal Function

Reduction of the dosage of lamivudine is recommended for patients with impaired renal function.

Tenofovir disoproxil fumarate

Pregnancy: Teratogenic Effects:

Pregnancy Category B

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

Nursing Mothers

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that tenofovir is secreted in milk. In humans, samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is excreted in human milk at low levels. The impact of this exposure in breastfed infants is unknown. Because of both the potential for

HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving Tenofovir disoproxil fumarate.

Pediatric Use

The safety of tenofovir disoproxil fumarate in pediatric patients aged 2 to less than 18 years is supported by data from two randomized trials in which tenofovir disoproxil fumarate was administered to HIV-1 infected treatment-experienced subjects. In addition, the pharmacokinetic
profile of tenofovir in patients 2 to less than 18 years of age at the recommended doses was similar to that found to be safe and effective in adult clinical trials.

In Study 352, 92 treatment-experienced subjects 2 to less than 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimen were randomized to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (N = 44) or continue their original regimen (N = 48) for 48 weeks. Five additional subjects over the age of 12 were enrolled and randomized (tenofovir disoproxil fumarate N=4, original regimen N=1) but are not included in the efficacy analysis. After 48 weeks, all eligible subjects were allowed to continue in the study receiving open-label tenofovir disoproxil fumarate. At week 48, 89% of subjects in the Tenofovir disoproxil fumarate treatment group and 90% of subjects in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations less than 400 copies/mL. During the 48 week randomized phase of the study, 1 subject in the tenofovir disoproxil fumarate group discontinued the study prematurely because of virologic failure/lack of efficacy and 3 subjects (2 subjects in the Tenofovir disoproxil fumarate group and 1 subject in the stavudine or zidovudine group) discontinued for other reasons.

In Study 321, 87 treatment-experienced subjects 12 to less than 18 years of age were treated with tenofovir disoproxil fumarate (N=45) or placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm3 and the mean baseline plasma HIV-1 RNA was 4.6 log10 copies/mL. At baseline, 90% of subjects harbored NRTI resistance-associated substitutions in their HIV-1 isolates. Overall, the trial failed to show a difference in virologic response between the tenofovir disoproxil fumarate and placebo treatment groups. Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to Tenofovir disoproxil fumarate and OBR.

Although changes in HIV-1 RNA in these highly treatment-experienced subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults

supports the use of tenofovir disoproxil fumarate in pediatric patients 12 years of age and older who weigh greater than or equal to 35 kg and whose HIV-1 isolate is expected to be sensitive to tenofovir disoproxil fumarate.

Safety and effectiveness of tenofovir disoproxil fumarate in pediatric patients younger than 2 years of age have not been established.

Geriatric Use

Clinical trials of tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Impaired Renal Function

It is recommended that the dosing interval for tenofovir disoproxil fumarate be modified in patients with creatinine clearance below 50 mL/min or in patients with ESRD who require dialysis.

4.7 Effects on ability to drive and use machines

Efavirenz

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

Lamivudine

No studies on the effects on the ability to drive and use machines have been performed.

Tenofovir disoproxil fumarate

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

4.8 Undesirable Effects

Efavirenz

The most significant adverse reactions observed in patients treated with efavirenz are:

• psychiatric symptoms,

• nervous system symptoms,

• rash.

The most common (>5% in either efavirenz treatment group) adverse reactions of at least moderate severity among patients in Study 006 treated with efavirenz in combination with zidovudine/lamivudine or indinavir were rash, dizziness, nausea, headache, fatigue, insomnia, and vomiting.

Clinical Trials Experience in Adults

Because clinical studies are conducted under widely varying conditions, the adverse reaction rates reported cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in clinical practice.

Selected clinical adverse reactions of moderate or severe intensity observed in □2% of efavirenztreated patients in two controlled clinical trials are presented in below.

Table: Selected Treatment-Emergenta Adverse Reactions of Moderate or Severe Intensity Reported in ≥ 2% of Efavirenz-Treated Patients in Studies 006 and ACTG 364

Adverse Reactions	**Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients**			**Study ACTG 364 NRTI-experienced, NNRTI-, and Protease Inhibitor-Naive Patients Efavirenz**		
	Efavirenz[b] + ZDV/LAM (n=412) 180 weeks[c]	Efavirenz[b] + Indinavir (n=415) 102 weeks[c]	Indinavir + ZDV/LAM (n=401) 76 weeks[c]	Efavirenzb + Nelfinavir + NRTIs (n=64) 71.1 weeks[c]	Efavirenz[b] + NRTIs (n=65) 70.9 weeks[c]	Nelfinavir + NRTIs (n=66) 62.7 weeks[c]
Body as a Whole						
Fatigue	8%	5%	9%	0	2%	3%
Pain	1%	2%	8%	13%	6%	17%
Central and Peripheral Nervous System						
Dizziness	9%	9%	2%	2%	6%	6%
Headache	8%	5%	3%	5%	2%	3%
Insomnia	7%	7%	2%	0	0	2%
Concentration impaired	5%	3%	<1%	0	0	0
Abnormal dreams	3%	1%	0	-	-	-

Somnolence	2%	2%	<1%	0	0	0
Anorexia	1%	<1%	<1%	0	2%	2%
Gastrointestinal						
Nausea	10%	6%	24%	3%	2%	2%
Vomiting	6%	3%	14%	-	-	-
Diarrhea	3%	5%	6%	14%	3%	9%
Dyspepsia	4%	4%	6%	0	0	2%
Abdominal pain	2%	2%	5%	3%	3%	3%
Psychiatric						
Anxiety	2%	4%	<1%	—	—	—
Depression	5%	4%	<1%	3%	0	5%
Nervousness	2%	2%	0	2%	0	2%
Skin& Appendages						
Rash[d]	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

[a] Includes adverse events at least possibly related to study drug or of unknown relationship for Study 006. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.

[b] Efavirenz provided as 600 mg once daily.

[c] Median duration of treatment.

[d] Includes erythema multiforme, rash, rash erythematous, rash follicular, rash maculopapular, rash petechial, rash pustular, and urticaria for Study 006 and macules, papules, rash, erythema, redness, inflammation, allergic rash, urticaria, welts, hives, itchy, and pruritus for ACTG 364.

— = Not Specified.

ZDV = zidovudine, LAM=lamivudine.

Pancreatitis has been reported, although a causal relationship with efavirenz has not been established. Asymptomatic increases in serum amylase levels were observed in a significantly higher number of patients treated with efavirenz 600 mg than in control patients.

Nervous System Symptoms

For 1008 patients treated with regimens containing efavirenz and 635 patients treated with a control regimen in controlled trials, below table lists the frequency of symptoms of different degrees of severity and gives the discontinuation rates for one or more of the following nervous system

symptoms: dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization. The frequencies of specific central and peripheral nervous system symptoms are provided in the above table.

Table: Percent of Patients with One or More Selected Nervous System Symptoms [a,b]

Percent of Patients with:	Efavirenz 600 mg Once Daily (n=1008) %	Control Groups (n=635) %
Symptoms of any severity	52.7	24.6
Mild symptoms[c]	33.3	15.6
Moderate symptomsd	17.4	7.7
Severe symptomse	2.0	1.3
Treatment discontinuation as a result of symptoms	2.1	1.1

[a] Includes events reported regardless of causality.

[b] Data from Study 006 and three Phase 2/3 studies.

[c] "Mild" = Symptoms which do not interfere with patient's daily activities.

[d] "Moderate" = Symptoms which may interfere with daily activities.

[e] "Severe" = Events which interrupt patient's usual daily activities.

Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials, psychiatric symptoms observed at a frequency of >2% among patients treated with efavirenz or control regimens, respectively, were depression (19%, 16%), anxiety (13%, 9%), and nervousness (7%, 2%).

Rash

For 1008 adult and 57 pediatric patients treated with regimens containing efavirenz and 635 patients treated with a control regimen in controlled trials, the frequency of rash by NCI grade and the discontinuation rates as a result of rash in clinical studies are provided in the below table.

Table: Percent of Patients with Treatment-Emergent Rash[a, b]

Percent of Patients with:	Description of Rash Grade[c]	Efavirenz 600 mg Once Daily Adults	Efavirenz Pediatric Patients	Control Groups Adults

		(n=1008) %	(n=57) %	(n=635) %
Rash of any grade	—	26.3	45.6	17.5
Grade 1 rash	Erythema, pruritus	10.7	8.8	9.8
Grade 2 rash	Diffuse maculopapular rash, dry desquamation	14.7	31.6	7.4
Grade 3 rash	Vesiculation, moist desquamation, ulceration	0.8	1.8	0.3
Grade 4 rash	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	0.1	3.5	0.0
Treatment discontinuation as a result of rash	—	1.7	8.8	0.3

[a] Includes events reported regardless of causality.

[b] Data from Study 006 and three Phase 2/3 studies.

[c] NCI Grading System.

As seen in above table, rash is more common in pediatric patients and more often of higher grade (ie, more severe).

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. Nine of these patients developed mild-to-moderate rash while receiving therapy with efavirenz, and two of these patients discontinued because of rash.

Laboratory Abnormalities

Selected Grade 3 to 4 laboratory abnormalities reported in ≥2% of efavirenz-treated patients in two clinical trials are presented in the below table.

Table: Selected Grade 3 to 4 Laboratory Abnormalities Reported in ≥2% of Efavirenz-Treated Patients in Studies 006 and ACTG 364

		Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			**Study ACTG 364 NRTI-experienced, NNRTI-, and Protease Inhibitor-Naive Patients**		
Variable Chemistry	Limit	Efavirenz[a] + ZDV/LAM (n=412) 180 weeks[b]	Efavirenz[a] + Indinavir (n=415) 102 weeks[b]	Indinavir + ZDV/LAM (n=401) 76 weeks[b]	Efavirenz[a] + Nelfinavir NRTIs (n=64) 71.1 weeks[b]	Efavirenz[a] + NRTIs (n=65) 70.9 weeks[b]	Nelfinavir + NRTIs (n=66) 62.7 weeks[b]
ALT	>5 x ULN	5%	8%	5%	2%	6%	3%
AST	>5 x ULN	5%	6%	5%	6%	8%	8%
GGT[C]	>5 x ULN	8%	7%	3%	5%	0	5%
Amylase	>2 x ULN	4%	4%	1%	0	6%	2%
Glucose	>250 mg/dL	3%	3%	3%	5%	2%	3%
Triglycerides[d]	≥751 mg/dL	9%	6%	6%	11%	8%	17%
Hematology Neutrophils	<750/mm^3	10%	3%	5%	2%	3%	2%

[a] Efavirenz provided as 600 mg once daily.

[b] Median duration of treatment.

[c] Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity.

[d] Nonfasting.

ZDV = zidovudine, LAM = lamivudine, ULN = Upper limit of normal, ALT = alanine aminotransferase,

AST = aspartate aminotransferase, GGT = gamma-glutamyltransferase.

Patients Coinfected with Hepatitis B or C

Liver function tests should be monitored in patients with a history of hepatitis B and/or C. In the long-term data set from Study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these coinfected patients, elevations in AST to greater than five times ULN developed in 13% of patients in the efavirenz arms and 7% of those in the control arm, and elevations in ALT to greater than five times ULN developed in 20% of patients in the Efavirenz arms and 7% of patients in the control arm. Among coinfected patients, 3% of those treated with efavirenz- containing regimens and 2% in the control arm discontinued from the study because of liver or biliary system disorders

Lipids

Increases from baseline in total cholesterol of 10 to 20% have been observed in some uninfected volunteers receiving efavirenz. In patients treated with efavirenz + zidovudine + lamivudine, increases from baseline in nonfasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with efavirenz + indinavir, increases from baseline in nonfasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed.

Nonfasting total cholesterol levels □240 mg/dL and □300 mg/dL were reported in 34% and 9%, respectively, of patients treated with efavirenz + zidovudine + lamivudine; 54% and 20%, respectively, of patients treated with efavirenz + indinavir; and 28% and 4%, respectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of efavirenz on triglycerides and LDL in this study were not well characterized since samples were taken from nonfasting patients. The clinical significance of these findings is unknown.

Clinical Trial Experience in Pediatric Patients

Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3 to 16 years who received efavirenz capsules, nelfinavir, and one or more NRTIs in Study ACTG 382 were rash (46%), diarrhea/loose stools (39%), fever (21%), cough (16%), dizziness/lightheaded/fainting (16%), ache/pain/discomfort (14%), nausea/vomiting (12%), and headache (11%). The incidence of nervous system symptoms was 18% (10/57). One patient experienced Grade 3 rash, two patients had Grade 4 rash, and five patients (9%) discontinued because of rash.

Post marketing Experience

The following adverse reactions have been identified during postapproval use of efavirenz. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: allergic reactions, asthenia, redistribution/accumulation of body fat Central and Peripheral Nervous System: abnormal coordination, ataxia, cerebellar coordination and balance disturbances, convulsions, hypoesthesia, paresthesia, neuropathy, tremor, vertigo

Endocrine: gynecomastia

Gastrointestinal: constipation, malabsorption

Cardiovascular: flushing, palpitations

Liver and Biliary System: hepatic enzyme increase, hepatic failure, hepatitis. A few of the postmarketing 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.

Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia

Musculoskeletal: arthralgia, myalgia, myopathy

Psychiatric: aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide

Respiratory: dyspnea

Skin and Appendages: erythema multiforme, photoallergic dermatitis, Stevens-Johnson syndrome

Special Senses: abnormal vision, tinnitus

Lamivudine

The following adverse reactions are discussed in greater detail in other sections of the labeling:

• Lactic acidosis and severe hepatomegaly with steatosis.

• Severe acute exacerbations of hepatitis B.

• Hepatic de-compensation in patients co-infected with HIV-l and Hepatitis C.

• Pancreatitis.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults - Clinical Trials in HIV-1: The safety profile of lamivudine in adults is primarily based on 3,568 HIV-l-infected patients in 7 clinical trials.

The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea and cough.

Selected clinical adverse reactions of in ≥5% of patients during therapy with lamivudine 150 mg twice daily plus RETROVIR® 200 mg 3 times daily for up to 24 weeks are listed in the below table.

Table: Selected Clinical Adverse Reactions (≥ 5% Frequency) in Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)

Adverse Reaction	Lamivudine 150 Twice Daily plus RETROVIR (n = 251)	RETROVIRa (n = 230)
Body as a Whole	35%	27%
Headache	27%	23%
Malaise & fatigue	10%	12%
Fever or chills		
Digestive	33%	29%
Nausea	18%	22%
Diarrhea	13%	12%
Nausea & vomiting	10%	7%
Anorexia and/o decreased appetite	9%	11%
Abdominal pain		

Adverse Reaction	Lamivudine 150 Twice Daily plus RETROVIR (n = 251)	RETROVIR[a] (n = 230)

Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous System	12%	10%
Neuropathy	11%	7%
Insomnia & other sleep disorders	10%	4%
Dizziness	9%	4%
Depressive disorders	20%	11%
Respiratory	18%	13%
Nasal signs & symptoms	9%	6%
Cough	12%	10%
Skin	8%	6%
Skin rashes	5%	5%
Musculoskeletal		
Musculoskeletal pain		
Myalgia		
Arthralgia		

[a] Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

Pancreatitis: Pancreatitis was observed in 9 out of 2,613 adult patients (0.3%) who received lamivudine in controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and NUCB3007.

Lamivudine 300 mg Once Daily: The types and frequencies of clinical adverse reactions reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) for 48 weeks were similar.

Selected laboratory abnormalities observed during therapy are summarized in the below table.

Table: Frequencies of Selected Grade 3 to 4 Laboratory Abnormalities in Adults in Four 24- Week Surrogate Endpoint Studies (NUCA3001, NUCA3002, NUCB3001, NUCB3002) and a Clinical End point Study (NUCB3007)

Test (Threshold Level)	24-Week Surrogate Endpoint Studiesa		Clinical Endpoint Studya	
	Lamivudine plus RETROVIR	RETROVIR[b]	Lamivudine plus Current Therapy	Placebo plus Current

				Therapy[c]
Absolute neutrophil count	7.2%	5.4%	15%	13%
(<750/mm3)	2.9%	1.8%	2.2%	3.4%
Hemoglobin (<8.0 g/dL)	0.4%	1.3%	2.8%	3.8%
Platelets (<50,000/mm3)	3.7%	3.6%	3.8%	1.9%
ALT (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
AST (>5.0 x ULN)	0.8%	0.4%	ND	ND
Bilirubin (>2.5 x ULN)	4.2%	1.5%	2.2%	1.1%
Amylase (>2.0 x ULN)				

[a] The median duration on study was 12 months.

[b] Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

[c] Current therapy was either zidovudine, zidovudine plus didonasine, or zidovudine plus zalcitabine

ULN = Upper limit of normal.

ND = Not done.

The frequencies of selected laboratory abnormalities reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar.

Pediatric Patients - Clinical Trials in HIV-1:

Selected clinical adverse reactions and physical findings with a ≥5% frequency during therapy with lamivudine 4 mg/kg twice daily plus RETROVIR 160 mg/m2 3 times daily in therapynaive (≤56 days of antiretroviral therapy) pediatric patients are listed in the below table.

Table: Selected Clinical Adverse Reactions and Physical Findings (≥5% frequency) in Pediatric Patients in Study ACTG300

Adverse Reaction	Lamivudine plus RETROVIR (n = 236)	Didanosine (n = 235)
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%

Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of earsa	7%	6%
Nasal discharge or congestion	8%	11%
Other	12%	14%
Skin rashes	9 %	11%
Lymphadenopathy		

[a] Includes pain, discharge, erythema, or swelling of an ear.

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these patients died of complications of pancreatitis. In a second open-label study (NUCA2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to lamivudine plus RETROVIR. Pancreatitis was observed in 1 patient in this study who received open- label lamivudine in combination with RETROVIR and ritonavir following discontinuation of didanosine monotherapy.

Paresthesias and Peripheral Neuropathies: Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study NUCA2002, 6 patients (9%) in Study NUCA2005, and 2 patients (<1%) in Study ACTG300.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in the below table.

Table: Frequencies of Selected Grade 3 to 4 Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Threshold Level)	Lamivudine plus RETROVIR	Didanosine

Absolute neutrophil count (<400/mm3)	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm3)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total Amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal.

Neonates - Clinical Trials in HIV-1: Limited short-term safety information is available from 2 small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at Week 38 or 36 of gestation. Selected adverse reactions reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, and sepsis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control groups limits assessments of causality, but it should be assumed that perinatally exposed infants may be at risk for adverse reactions comparable to those reported in pediatric and adult HIV-1-infected patients treated with lamivudine containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

Post marketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been reported during postmarketing use of lamivudine. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine.

Body as a Whole: Redistribution/accumulation of body fat.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy).

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, posttreatment exacerbation of hepatitis B.

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Skin: Alopecia, pruritus.

Tenofovir Disoproxil Fumarate

The following adverse reactions are discussed in other sections of the labeling:

• Lactic acidosis/Severe Hepatomegaly with Steatosis.

• Severe Acute Exacerbation of Hepatitis.

• New Onset or Worsening Renal Impairment.

• Decreases in Bone Mineral Density.

• Immune Reconstitution Syndrome.

Adverse Reactions from Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adult Patients with HIV-1 Infection

More than 12,000 subjects 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 clinical trials and expanded access programs. A total of 1,544 subjects have received Tenofovir disoproxil fumarate 300 mg once daily in clinical trials; over 11,000 subjects have received tenofovir disoproxil fumarate in expanded access programs.

The most common adverse reactions (incidence greater than or equal to 10%, Grades 2 to 4) identified from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

Treatment-Naïve Patients

Study 903 - Treatment-Emergent Adverse-Reactions: The most common adverse reactions seen in a double-blind comparative controlled trial in which 600 treatment-naïve subjects received tenofovir

disoproxil fumarate (n=299) or stavudine (n=301) in combination with lamivudine and efavirenz for 144 weeks (study 903) were mild to moderate gastrointestinal events and dizziness.

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse reactions are summarized in the below table.

Table: Selected Treatment-Emergent Adverse Reactionsa (Grades 2 to 4) Reported in 5% in Any Treatment Group in Study 903 (0 to 144 Weeks)

	Tenofovir Disoproxil fumarate+ 3TC + EFV	**d4T + 3TC + EFV**
	N=299	**N=301**
Body as a whole		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal pain	7%	12%
Back pain	9%	8%
Asthenia	6%	7%
Digestive system		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
vomiting	5%	9%
Metabolic disorders Lipodystrophy[b]	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous system		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%

Peripheral neuropathyc Anxiety	1% 6%	5% 6%
Respiratory Pneumonia	5%	5%
Skin and Appendages Rash event[d]	18%	12%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

b. Lipodystrophy represents a variety of investigator-described adverse events not a protocoldefined syndrome.

c. Peripheral neuropathy includes peripheral neuritis and neuropathy.

d. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with Tenofovir disoproxil fumarate (19% and 1%) respectively, laboratory abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms.

A summary of grade 3 and 4 laboratory abnormalities is provided in the below table.

Table: Grade 3/4 Laboratory Abnormalities Reported in 1% of Tenofovir Disoproxil Fumarate-Treated Subjects in Study 903 (0 to 144 weeks)

	Tenofovir disoproxil fumarate + 3TC + EFV	**d4T + 3TC + EFV**
	N=299	**N = 301**
Any Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (>240 mg/dL)	19%	40%
Creatine Kinase (M: >990 U/L; F:	12%	12%

Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L; F: >170 U/L)	5%	7%
ALT (M: >215 U/L; F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophils (<750/mm3)	3%	1%
Fasting Triglycerides (>750 mg/dL)	1%	9%

Study 934 - Treatment Emergent Adverse Reactions: In study 934, 511 antiretroviral-naïve subjects received either tenofovir disoproxil fumarate + EMTRIVA® administered in combination with Efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this trial were generally consistent with those seen in previous studies in treatment experienced or treatment-naïve subjects.

Table: Selected Treatment-Emergent Adverse Reactions[a] (Grades 2 to 4) Reported in 5% in Any Treatment Group in Study 934 (0 to 144 weeks)

	Tenofovir disoproxil fumarate[b] + FTC + EFV	**AZT/3TC + EFV**
	N=257	**N=254**
Gastrointestinal Disorder		
Diarrhea	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	9%	7%

Depression Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders Rash event[c]	7%	9%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

b. From weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of tenofovir disoproxil fumarate + EMTRIVA with efavirenz.

c. rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculopapular, rash pruritic, and rash vesicular.

Laboratory Abnormalities: Laboratory abnormalities observed in this trial were generally consistent with those seen in previous trials.

Table: Significant Laboratory Abnormalities Reported in 1% of Subjects in Any Treatment Group in Study 934 (0 to 144 weeks)

	Tenofovir disoproxil fumarate[a] + FTC + EFV	**AZT/3TC + EFV**
	N=257	**N=254**
Any Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L; F: >170 U/L)	3%	3%
ALT (M: >215 U/L; F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%

Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria(3+)	<1%	1%
Neutrophils (<750/mm3)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

a. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of Tenofovir disoproxil fumarate + EMTRIVA with efavirenz.

Treatment-Experienced Patients

Treatment-Emergent Adverse Reactions: The adverse reactions seen in treatment experienced subjects were generally consistent with those seen in treatment naïve subjects including mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of subjects discontinued participation in the clinical trials due to gastrointestinal adverse reactions (Study 907).

A summary of moderate to severe, treatment-emergent adverse reactions that occurred during the first 48 weeks of study 907 is provided in the below table.

Table: Selected Treatment-Emergent Adverse Reactionsa (Grades 2 to 4) Reported in 3% in Any Treatment Group in Study 907 (0 to 48 Weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0 - 24)	**Placebo (N=182) (Week 0 -24)**	**Tenofovir disoproxil fumarate (N=368) (Week 0 - 48)**	**Placebo Crossover to Tenofovir disoproxil fumarate (N=170) (Week 24 - 48)**
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal pain	4%	3%	7%	6%
Back pain	3%	3%	4%	2%
Chest pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
	3%	2%	4%	2%

Dyspepsia Flatulence	3%	1%	4%	1%
Respiratory Pneumonia	2%	0%	3%	2%
Nervous System Depression Insomnia Peripheral neuropathy[b] Dizziness	 4% 3% 3% 1%	 3% 2% 3% 3%	 8% 4% 5% 3%	 4% 4% 2% 1%
Skin and Appendage Rash event[c] Sweating	 5% 3%	 4% 2%	 7% 3%	 1% 1%
Musculoskeletal Myalgia	3%	3%	4%	1%
Metabolic Weight loss	2%	1%	4%	2%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

b. Peripheral neuropathy includes peripheral neuritis and neuropathy.

c. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: Laboratory abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in the below table.

Table: Grade 3/4 Laboratory Abnormalities Reported in 1% of Tenofovir Disoproxil Fumarate-Treated Subjects in Study 907 (0 to 48 Weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0 - 24)	**Placebo (N=182) (Week 0 - 24)**	**Tenofovir disoproxil fumarate (N=368) (Week 0 - 48)**	**Placebo crossover to Tenofovir disoproxil fumarate (N=170) (Week 24 - 48)**
Any Grade 3 Laboratory Abnormality	25%	38%	35%	34%

Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine kinase (M: >990 U/L; F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Glycosuria (≥3+)	3%	3%	3%	2%
AST (M: >180 U/L; F:>170 U/L)	3%	3%	4%	5%
ALT (M: >215 U/L; F: >170 U/L)	2%	2%	4%	5%
Serum Glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750/mm3)	1%	1%	2%	1%

Clinical Trials in Pediatric Subjects 2 Years of Age and Older with HIV-1 Infection

Assessment of adverse reactions is based on two randomized trials (Studies 352 and 321) in 184 HIV-1 infected pediatric subjects (2 to less than 18 years of age) who received treatment with tenofovir disoproxil fumarate (N=93) or placebo/active comparator (N=91) in combination with other antiretroviral agents for 48 weeks. The adverse reactions observed in subjects who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical trials in adults.

Bone effects observed in pediatric subjects 2 years of age and older were consistent with those observed in adult clinical trials.

Eighty-nine pediatric subjects received tenofovir disoproxil fumarate in Study 352 (48 who were initially randomized to tenofovir disoproxil fumarate and 41 who were initially randomized to continue stavudine or zidovudine and then received tenofovir disoproxil fumarate in the extension phase) for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these 4 subjects presented with hypophosphatemia and also had decreases in total body or spine BMD Z score. Clinical Trials in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease

Treatment-Emergent Adverse Reactions: In controlled clinical trials in subjects with chronic hepatitis B (0102 and 0103), more subjects treated with tenofovir disoproxil fumarate during the 48-week double-blind period experienced nausea: 9% with tenofovir disoproxil fumarate versus 2% with HEPSERA. Other treatment-emergent adverse reactions reported in more than 5% of subjects treated with tenofovir disoproxil fumarate included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash.

During the open-label phase of treatment with tenofovir disoproxil fumarate (weeks 48 to 192) in Studies 0102 and 0103, less than 1% of subjects (5/585) experienced a confirmed increase in serum creatinine of 0.5 mg/dL from baseline. No significant change in the tolerability profile was observed with continued treatment for up to 192 weeks.

Laboratory Abnormalities: A summary of Grade 3 and 4 laboratory abnormalities through Week 48 is provided in Table 16. Grade 3/4 laboratory abnormalities were similar in subjects continuing tenofovir disoproxil fumarate treatment for up to 192 weeks in these trials.

Table: Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate - Treated Subjects in Studies 0102 and 0103 (0 to 48 Weeks)

	Tenofovir disoproxil fumarate (N=426)	**HEPSERA (N=215)**
Any Grade 3 Laboratory Abnormality	19%	13%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	2%	3%
Serum Amylase (>175 U/L)	4%	1%
Glycosuria (≥3+)	3%	<1%

The overall incidence of on-treatment ALT flares (defined as serum ALT greater than 2 × baseline and greater than 10 × ULN, with or without associated symptoms) was similar between Tenofovir disoproxil fumarate (2.6%) and HEPSERA (2%). ALT flares generally occurred within the first 4 to 8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No subject had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in study medication.

Clinical Trials in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Disease

In a small randomized, double-blind, active-controlled trial (0108), subjects with CHB and decompensated liver disease received treatment with tenofovir disoproxil fumarate or other antiviral drugs for up to 48 weeks. Among the 45 subjects receiving tenofovir disoproxil fumarate, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the trial due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus less than 2 mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score greater than or equal to 10 and MELD score greater than or equal to 14 at entry) developed renal failure. Because both tenofovir disoproxil fumarate and decompensated liver disease may have an impact on renal function, the contribution of Tenofovir disoproxil fumarate to renal impairment in this population is difficult to ascertain.

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

Post marketing Experience

The following adverse reactions have been identified during post approval use of Tenofovir disoproxil fumarate. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Immune System Disorders
- Allergic reaction, including angioedema
- Metabolism and Nutrition Disorders
- Lactic acidosis, hypokalemia, hypophosphatemia
- Respiratory, Thoracic, and Mediastinal Disorders
- Dyspnea
- Gastrointestinal Disorders
- Pancreatitis, increased amylase, abdominal pain
- Hepatobiliary 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, osteomalacia (manifested as bone pain and which may contribute to fractures),
- muscular weakness, myopathy
- Renal and Urinary Disorders
- Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal
- tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal
- insufficiency, increased creatinine, proteinuria, polyuria
- General Disorders and Administration Site Conditions
- Asthenia
- The following adverse reactions, listed under the body system headings above, may occur as a
- consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular
- weakness, myopathy, hypophosphatemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the authority ADR reporting tool; search for authority Adverse Reactions Reporting Tool in the Google Play Store.

4.9 Overdose

Efavirenz

Some patients accidentally taking 600 mg 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 antidote for lamivudine. One case of an adult ingesting 6 g of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in Study ACTG300. One case involved a single dose of 7 mg/kg of lamivudine; the second case involved use of 5 mg/kg
of lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. 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. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

Tenofovir disoproxil fumarate

Limited clinical experience at doses higher than the therapeutic dose of tenofovir Disoproxil fumarate 300 mg is available. In study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

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 disoproxil fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Efavirenz

Microbiology

Mechanism of Action

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

Antiviral Activity in Cell Culture

The concentration of EFV inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90 to 95% (EC90 to 95) ranged from 1.7 to 25 nM in lymphoblastoid cell lines,

peripheral blood mononuclear cells (PBMCs), and macrophage/monocyte cultures. EFV 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. EFV demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine (DLV) and nevirapine (NVP), NRTIs (abacavir, didanosine, emtricitabine, lamivudine [LAM], stavudine, tenofovir, zalcitabine, zidovudine [ZDV]), PIs (amprenavir, indinavir [IDV], lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. EFV demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. EFV 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 EFV (>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 RT.

Clinical studies

Clinical isolates with reduced susceptibility in cell culture to EFV have been obtained. One or more RT substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, and 227 were observed in patients failing treatment with EFV in combination with IDV, or with ZDV plus LAM.

The mutation K103N was the most frequently observed. Long-term resistance surveillance (average 52 weeks, range 4 to 106 weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one percent (17/28) of these failure isolates had decreased EFV susceptibility in cell culture with a median 88-fold change in EFV susceptibility (EC50 value) from reference. The most frequent NNRTI substitution to develop in these patient isolates was K103N (54%). Other NNRTI substitutions that developed included L100I (7%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%).

Cross-Resistance

Cross-resistance among NNRTIs has been observed. Clinical isolates previously characterized as EFV-resistant were also phenotypically resistant in cell culture to DLV and NVP compared to baseline. DLV- and/or NVP-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 EFV in cell culture. Greater than 90% of NRTIresistant clinical isolates tested in cell culture retained susceptibility to EFV.

Lamivudine:

Microbiology

Mechanism of Action: Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases α, β, and γ.

Antiviral Activity: The antiviral activity of lamivudine against HIV-l was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC50 values (50% effective concentrations) were in the range of 0.003 to 15μM (l μM = 0.23 mcg/mL). HIV-l from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC50 values of 0.429 μM (range: 0.200 to 2.007 μM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 μM (1.37 to 3.68 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC50 values of lamivudine against different HIV-l clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV-1- infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. Please see the full prescribing information for EPIVIR-HBV for information regarding the inhibitory activity of lamivudine against HBV.

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 isoleucine or valine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine resistant virus at baseline, phenotypic sensitivity to

zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Lamivudine-resistant HBV isolates develop substitutions (rtM204V/I) in the YMDD motif of the catalytic domain of the viral reverse transcriptase. rtM204V/I substitutions are frequently accompanied by other substitutions (rtV173L, rtL180M) which enhance the level of lamivudine resistance or act as compensatory mutations improving replication efficiency.

Other substitutions detected in lamivudine-resistant HBV isolates include: rtL80I and rtA181T.

Similar HBV mutants have been reported in HIV-1-infected patients who received lamivudine containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Cross-Resistance: Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates From Patients with Virologic Failure: Study EPV20001: Fifty-three of 554 (10%) patients enrolled in EPV20001 were identified as virological failures (plasma HIV-l RNA level ≥400 copies/mL) by Week 48. Twenty-eight patients were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-l RNA levels of patients in the lamivudine once-daily group and lamivudine twice-daily group were 4.9 log10 copies/mL and 4.6 log10 copies/mL, respectively.

Genotypic analysis of on-therapy isolates from 22 patients identified as virologic failures in the lamivudine once-daily group showed that isolates from 0/22 patients contained treatment emergent amino acid substitutions associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E), isolates from 10/22 patients contained treatment emergent amino acid substitutions associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C), and isolates from 8/22 patients contained a treatment-emergent lamivudine resistance-associated substitution (M184I or M184V).

Genotypic analysis of on-therapy isolates from patients (n = 22) in the lamivudine twice-daily treatment group showed that isolates from 1/22 patients contained treatment-emergent zidovudine resistance substitutions, isolates from 7/22 contained treatment-emergent efavirenz resistance substitutions, and isolates from 5/22 contained treatment-emergent lamivudine resistance substitutions.

Phenotypic analysis of baseline-matched on-therapy HIV-l isolates from patients (n =13) receiving lamivudine once daily showed that isolates from 12/13 patients were susceptible to zidovudine; isolates

from 8/13 patients exhibited a 25- to 295-fold decrease in susceptibility to efavirenz, and isolates from 7/13 patients showed an 85- to 299-fold decrease in susceptibility to lamivudine.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n=13) receiving lamivudine twice daily showed that isolates from all 13 patients were susceptible to zidovudine; isolates from 3/13 patients exhibited a 21- to 342-fold decrease in susceptibility to efavirenz, and isolates from 4/13 patients exhibited a 29- to 159-fold decrease in susceptibility to lamivudine. Study EPV40001: Fifty patients received zidovudine 300 mg twice daily plus abacavir 300 mg twice daily plus lamivudine 300 mg once daily and 50 patients received zidovudine 300 mg plus abacavir 300 mg plus lamivudine 150 mg all twice daily. The median baseline plasma HIV-1 RNA levels for patients in the 2 groups were 4.79 log10 copies/mL and 4.83 log10 copies/mL, respectively. Fourteen of 50 patients in the lamivudine once-daily treatment group and 9 of 50 patients in the lamivudine twice-daily group were identified as virologic failures.

Genotypic analysis of on-therapy HIV-1 isolates from patients (n = 9) in the lamivudine once-daily treatment group showed that isolates from 6 patients had an abacavir and/or lamivudine resistance-associated substitution M184V alone. On-therapy isolates from patients (n = 6) receiving lamivudine twice daily showed that isolates from 2 patients had M184V alone and isolates from 2 patients harbored the M184V substitution in combination with zidovudine resistance-associated amino acid substitutions.

Phenotypic analysis of on-therapy isolates from patients (n = 6) receiving lamivudine once daily showed that HIV-l isolates from 4 patients exhibited a 32- to 53-fold decrease in susceptibility to lamivudine. HIV-1 isolates from these 6 patients were susceptible to zidovudine.

Phenotypic analysis of on-therapy isolates from patients (n = 4) receiving lamivudine twice daily showed that HIV-l isolates from 1 patient exhibited a 45-fold decrease in susceptibility to lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

Tenofovir Disoproxil Fumarate

Microbiology

Mechanism of Action

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate 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 of tenofovir 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), additive to synergistic effects were observed. 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 2 to 4 fold reduction in susceptibility to tenofovir.

In Study 903 of treatment-naïve subjects (tenofovir disoproxil fumarate + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz), genotypic analyses of isolates from subjects with virologic failure through week 144 showed development of efavirenz and lamivudine resistance associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) analyzed patient isolates on the Tenofovir disoproxil fumarate arm and in 2/49 (4%) analyzed patient isolates on the stavudine arm. Of the 8 subjects whose virus developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and one at Week 96. Other substitutions resulting in resistance to tenofovir disoproxil fumarate were not identified in this trial.

In Study 934 of treatment-naïve subjects (tenofovir disoproxil fumarate + EMTRIVA + Efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz), genotypic analysis performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at week 144 or early discontinuation showed development of efavirenz resistance-associated substitutions occurred most

frequently and was similar between the two treatment arms. The M184V substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 analyzed subject isolates in the tenofovir disoproxil fumarate + EMTRIVA group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

Cross- Resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R substitution selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV-1 isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R substitution. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 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.

In Studies 902 and 907 conducted in treatment-experienced subjects (tenofovir disoproxil fumarate + Standard Background Therapy (SBT) compared to Placebo + SBT), 14/304 (5%) of the Tenofovir disoproxil fumarate-treated subjects with virologic failure through Week 96 had greater than 1.4- fold (median 2.7-fold) reduced susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R substitution in the HIV-1 reverse transcriptase gene.

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment-experienced subjects participating in studies 902 and 907. In these clinical trials, 94% of the participants evaluated had baseline HIV-1 isolates expressing at least one NRTI mutation. Virologic responses for subjects in the genotype substudy were similar to the overall trial results.

Several exploratory analyses were conducted to evaluate the effect of specific substitutions and substitutional patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross-resistance of tenofovir Disoproxil fumarate to pre-existing zidovudine resistance-associated substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) were observed and appeared to depend on the type and number of specific substitutions. Tenofovir disoproxil fumarate-treated subjects whose HIV-1 expressed 3 or more zidovudine resistance-associated substitutions that included either the M41L or L210W reverse transcriptase substitution showed reduced responses to tenofovir disoproxil fumarate therapy; however, these responses were still improved

compared with placebo. The presence of the D67N, K70R, T215Y/F, or K219Q/E/N substitution did not appear to affect responses to Tenofovir disoproxil fumarate therapy. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to tenofovir Disoproxil fumarate. Limited data are available for subjects whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

In the protocol defined analyses, virologic response to tenofovir disoproxil fumarate was not reduced in subjects with HIV-1 that expressed the abacavir/emtricitabine/lamivudine resistance associated M184V substitution. HIV-1 RNA responses among these subjects were durable through week 48.

Studies 902 and 907 Phenotypic Analyses

Phenotypic analysis of baseline HIV-1 from treatment-experienced subjects (N=100) demonstrated a correlation between baseline susceptibility to tenofovir disoproxil fumarate and response to tenofovir disoproxil fumarate therapy. Below table summarizes the HIV-1 RNA response by baseline tenofovir disoproxil fumarate susceptibility.

Table: HIV-1 RNA Response at Week 24 by Baseline Tenofovir Disoproxil Fumarate Susceptibility (Intent-To-Treat)[a]

Baseline Tenofovir Disoproxil Fumarate Susceptibility[b]	Change in HIV-1 RNA[C] (N)
<1	-0.74 (35)
>1 and ≤3	-0.56 (49)
>3 and ≤4	-0.3 (7)
>4	-0.12 (9)

a. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).

b. Fold change in susceptibility from wild-type.

c. Average HIV-1 RNA change from baseline through Week 24 (DAVG24) in log10 copies/mL.

Activity against HBV

Antiviral Activity

The antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC_{50} values for tenofovir ranged from 0.14 to 1.5 μM, with CC50 (50% cytotoxicity concentration) values greater than 100 μM. In cell culture combination antiviral activity studies of tenofovir with the nucleoside

HBV reverse transcriptase inhibitors entecavir, lamivudine and telbivudine, and with the nucleoside HIV-1 reverse transcriptase inhibitor emtricitabine, no antagonistic activity was observed.

Resistance

Cumulative tenofovir disoproxil fumarate genotypic resistance has been evaluated annually for up to 192 weeks in Studies 0102, 0103, 0106, and 0108 with the paired HBV reverse transcriptase amino acid sequences of the pre-treatment and on-treatment isolates from subjects who received at least 24 weeks of tenofovir disoproxil fumarate monotherapy and remained viremic with HBV DNA greater than or equal to 400 copies/mL at the end of each study year (or at discontinuation of tenofovir disoproxil fumarate monotherapy) using an as-treated analysis. In the nucleotide-naïve population from Studies 0102 and 0103, HBeAg-positive subjects had a higher baseline viral load than HBeAg-negative subjects and a significantly higher proportion of the subjects remained viremic at their last time point on tenofovir disoproxil fumarate monotherapy (14% versus 4.1%, respectively).

HBV isolates from these subjects who remained viremic showed treatment-emergent substitutions; however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to tenofovir disoproxil fumarate (genotypic and phenotypic analyses).

Table: Amino Acid Substitutions in Viremic Subjects across HBV Trials of Tenofovir Disoproxil Fumarate

	Compensated Liver Disease		**Decompensated Liver Disease (N=39)[c]**
	Nucleotidenaïve (N=417)[a]	**Hepseraexperienced (N=247)[b]**	
Viremic at Last Time Point on Tenofovir Disoproxil Fumarate	34/417 (8%)	32/247 (13%)	7/39 (18%)
Treatment-Emergent Amino Acid Substitutions[d]	17[c]/31 (55%)	10/27 (37%)	3/5 (60%)

a. Nucleotide-naïve subjects from Studies 0102 (N=246) and 0103 (N=171) receiving up to 192 weeks of treatment with tenofovir disoproxil fumarate.

b. HEPSERA-experienced subjects from Studies 0102/0103 (N=195) and 0106 (N=52) receiving

up to 168 weeks of treatment with tenofovir disoproxil fumarate after switching to tenofovir disoproxil fumarate from HEPSERA. Study 0106, a randomized, double blind, 168-week Phase 2 trial, has been completed.

c. Subjects with decompensated liver disease from Study 0108 (N=39) receiving up to 48 weeks of treatment with tenofovir disoproxil fumarate.

d. Denominator includes those subjects who were viremic at last time point on tenofovir disoproxil fumarate monotherapy and had evaluable paired genotypic data.

e. Of the 17 subjects with treatment-emergent amino acid substitutions during Studies 0102 and 0103, 8 subjects had only transient substitutions that were not detected at the last time point on tenofovir disoproxil fumarate.

Cross -Resistance

Cross-resistance has been observed between HBV nucleoside/nucleotide analogue reverse transcriptase inhibitors.

In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V substitutions associated with resistance to lamivudine and telbivudine showed a susceptibility to Tenofovir ranging from 0.7 to 3.4-fold that of wild type virus. The rtL180M and rtM204I/V double substitutions conferred 3.4-fold reduced susceptibility to tenofovir.

HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V, and rtM250V substitutions associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6 to 6.9- fold that of wild type virus.

HBV strains expressing the adefovir resistance-associated substitutions rtA181V and/or rtN236T showed reductions in susceptibility to tenofovir ranging from 2.9 to 10-fold that of wild type virus.

Strains containing the rtA181T substitution showed changes in susceptibility to tenofovir ranging from 0.9 to 1.5-fold that of wild type virus.

Thirty-one subjects initiating tenofovir disoproxil fumarate therapy in Studies 0102, 0103, 0106, and 0108 harbored HBV with known resistance substitutions to HBV nucleos(t)ide analogue reverse transcriptase inhibitors: 14 with adefovir resistance-associated substitutions (rtA181T/V and/or rtN236T), 15 with lamivudine resistance-associated substitutions (rtM204I/V), and 2 with both adefovir and lamivudine resistance-associated substitutions. Following up to 192 weeks of tenofovir disoproxil fumarate treatment, 11 of the 14 subjects with adefovir-resistant HBV, 12 of the 15 subjects with lamivudine-resistant HBV,

and 1 of the 2 subjects with both adefovir- and lamivudine-resistant HBV achieved and maintained virologic suppression (HBV DNA less than 400 copies/mL). Three of the 5 subjects whose virus harbored both the rtA181T/V and rtN236T substitutions remained viremic.

5.2 Pharmacokinetic properties

Efavirenz

Pharmacokinetics

Absorption

Peak efavirenz plasma concentrations of 1.6 to 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 Cmax, 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 to 5 hours and steady-state plasma concentrations were reached in 6 to 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.

Effect of Food on Oral Absorption:

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∞ of efavirenz and a 79% increase in mean Cmax of efavirenz relative to the exposures achieved under fasted conditions.

Distribution

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.

Metabolism

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 to 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 to 42% lower) and a shorter terminal half-life of 40 to 55 hours (single dose half-life 52 to 76 hours).

Elimination

Efavirenz has a terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses. A one-month mass balance/excretion study was conducted using 400 mg per day with a 14C-labeled dose administered on Day 8. Approximately 14 to 34% of the radiolabel was recovered in the urine and 16 to 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.

Special Populations

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

Renal impairment: 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.

Hepatic impairment: 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

Drug Interaction Studies

Efavirenz has been shown in vivo to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A and CYP2B6. In vitro studies have shown that efavirenz inhibited CYP isozymes 2C9, 2C19, and 3A4 with Ki 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 (Ki values 82 to 160 μM) only at concentrations well above those achieved clinically. The inhibitory effect on CYP3A is expected to be similar between 200-mg, 400-mg,

and 600-mg doses of efavirenz. Co-administration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A isozymes may result in altered plasma concentrations of the co-administered drug. Drugs which induce CYP3A activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interaction studies were performed with efavirenz and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of efavirenz on the Cmax, AUC, and Cmin are summarized in below tables (effect of efavirenz on other drugs) and (effect of other drugs on efavirenz).

Table: Effect of Efavirenz on Coadministered Drug Plasma Cmax, AUC, and Cmin

Co administered Drug	**Dose**	**Efavirenz Dose**	**Number of Subjects**	**Coadministered Drug (mean % change)**		
				Cmax (90% CI)	**AUC (90% CI)**	**Cmin (90% CI)**
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓ 59% (49-67%)	↓ 74% (68-78%)	↓ 93% (90-95%)
	400 mg qd d 1-6, then 300 mg qd d 7-20 with ritonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7-20	13 ↓	↑ 14%a (↓ 17-↑ 58%)	↑ 39%a (2-88%)	↑ 48%a (24-76%)
	300 mg qd/ritonavir 100 mg qd d 1-10 (pm), then 400 mg qd/ritonavir 100 mg qd d 11-24 (pm) (simultaneous with efavirenz)	600 mg qd with a light snack d 11-24 (pm)	14	↑ 17% (8-27%)	↔	↓ 42% (31-51%)
Indinavir	1000 mg q8h x 10 days	600 mg qd x 10 days	20			

	After morning dose After afternoon dose After evening Dose			↔ [b] ↔ [b] ↓ 29%[b] (11-43%)	↓ 33% [b] (26-39%) ↓ 37% [b] (26-46%) ↓ 46 [b] (37-54%)	↓ 39% [b] (2451%) ↓ 52% [b] (47-57%) ↓ 57% [b] (50-63%)

Coadministered Drug	**Dose**	**Efavirenz Dose**	**Number of Subjects**	**Coadministered Drug (mean % change)**		
				Cmax (90% CI)	**AUC (90% CI)**	**Cmin (90% CI)**
Lopinavir/ ritonavir	400/100 mg capsule q12 h x 9 days	600 mg qd x 9 days	11,7[c]	↔[d]	↓ 19%[d] (↓ 36-↑ 3%)	↓ 39%[d] (3-62 %)
	tablet q12 10 days with efavirenz compared 400/100 mg	9 days	23	(28-44%)	(28-44%)	(21-44%)
	q12 h alone					

Nelfinavir Metabolite AG-1402	750 mg q8 h x 7 days	600 mg qd x 7 days	10	↑ 21% (10-33%) ↓ 40% (30-48%)	↑ 20% (8-34%) ↓ 37% (25-48%)	↔ ↓ 43% (21-59%)
Ritonavir	500 mg q12h x 8 days After AM dose After PM dose	600 mg qd x10 days	11	↑ 24% (12-38%) ↓ 40% (30-48%)	↑ 18% (6-33%) ↔	↑ 42% (9-86%) ↓24% (3-50%)
Saquinavir SGC[f]	1200 mg q8h x 10 days	600 mg qd x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%)e
Lamivudine	150 mg q12h x 14 days	600 mg qd x	9	↔	↔	↔

Tenofovir[g]	300 mg qd	600 mg qd x 14 days	29	↔	↔	↔
Zidovudine	300 mg q12h x 14 days	600 mg qd x 14 days	9	↔	↔	↑ 225% (43-640%)
Maraviroc	100 mg bid	600 mg qd	12	↓ 51% (37-62%)	↓ 45% (38-51%)	↓ 45% (28-57%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↑ 22% (4-42%)	↔	NA
Clarithromycin 14-OH metabolite	500 mg q12h x 7 days	400 mg qd x 7 days	11	↓ 26% (15-35%) ↑ 49% (32-69%)	↓ 39% (30-46%) ↑ 34% (18-53%)	↓ 53% (42-63%) ↑ 26% (9-45%)
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↔	↔

Itraconazole itraconazole	200 mg q12h x 28 days	600 mg qd x 14 days	18	↓ 37% (20-51%) (12-52%)	↓ 39% (21-53%) (14-55%)	↓ 44% (27-58%) (18-60%)

Coadministered Drug	**Dose**	**Efavirenz Dose**	**Number of Subjects**	**Coadministered Drug (mean % change)**		
				Cmax (90% CI)	**AUC (90% CI)**	**Cmin (90% CI)**
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg qd x 10 and 20 days	11	↓ 45% (34-53%)	↓ 50% (40-57%)	NA
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	9	↓ 32% (15-46%)	↓ 38% (28-47%)	↓ 45% (31-56%)
Voriconazole	400 mg po q12h x 1day, then 200 mg po q 12h x 8 days 300 mg po q12h days 2-7 400 mg po q12h days 2-7	400 mg qd x 9 days 300 mg qd x 7 days 300 mg qd x 7 days	NA NA NA	↓ 61%[ii] ↓ 36%[i] (21-49%) ↑ 23%i (↓ 1-↑53%)	↓ 77%[ii] ↓ 55%[i] (45-62%) ↓ 7%i (↓23-↑13%)	NA NA NA

Atorvastatin Total active (including metabolites)	10 mg qd x 4 days	600 mg qd x 15 days	14	↓ 14% (1-26%) ↓ 15% (2-26%)	↓ 43% (34-50%) ↓ 32% (21-41%)	↓ 69% (49-81%) ↓ 48% (23-64%)
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	13	↓ 32% (↓ 59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin Total active (including metabolites)	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 72% (63-79 %) ↓ 68 % (55-78 %)	↓ 68% (62-73 %) ↓ 60 % (52-68 %)	↓45% (20-62 %) NA[j]
Carbamazepine Epoxide metabolite	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days	600 mg qd x 14 days	12	↓ 20% (15-24%) ↔	↓ 27% (20-33%) ↔	↓ 35% (24-44%) ↓ 13% (↓ 30 - ↑7%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↓ 24% (18-30%)	↔	NA

Coadministered Drug	**Dose**	**Efavirenz Dose**	**Number of Subjects**	**Coadministered Drug (mean % change)**		
				Cmax (90% CI)	**AUC (90% CI)**	**Cmin (90% CI)**
Diltiazem	240 mg x 21	600 mg qd	13	↓ 60%	↓ 69%	↓ 63%

	days	14 days		(50-68%)	(55-79%)	(44-75%)
Desacetvl diltiazem				↓ 64%	↓ 75%	↓ 62%
N-mono				(57-69%)	(59-84%)	(44-75%)
desmethyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol/ Norgestimate	0.035 mg/0.25 mg x 14 days	600 mg qd x 14 days				
Norelgestromin			21	↓ 46%	↓64%	↓82%
				(39-52%)	(62-67%)	(79-85%)
Levonorgestrel			6	↓ 80% (77-83%)	↓ 83% (79-87%)	↓ 86% (80-90%)
Lorazepam	2 mg single dose	600 mg qd x	12	↑ 16%	↔	NA

		10 days		(2-32%)		
Methadone	Stable maintenance 35-100 mg daily	600 mg qd x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Bupropion	150 mg single (sustained-release)	600 mg qd x14 days	13	↓ 34% (21-	↓ 55% 62%) ↔	NA
Hydroxy-bupropion				↑ 50% (20-80%)		NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	16	↔	↔	↔

Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↓ 29% (15-40%)	↓ 39% (27-50%)	↓ 46% (31-58%)

↑ Indicates increase ↓Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%

[a] Compared with atazanavir 400 mg qd alone.

[b] Comparator dose of indinavir was 800 mg q8h x 10 days.

[c] Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for lopinavir/ritonavir alone.

[d] Values are for lopinavir, the pharmacokinetics of ritonavir in this study were unaffected by concurrent efavirenz.

[e] 95% CI.

[f] Soft Gelatin Capsule.

Table: Effect of Coadministered Drug on Efavirenz Plasma Cmax, AUC, and Cmin

				Efavirenz (mean % change)		
Coadministered Drug	**Dose**	**Efavirenz Dose**	**Number of Subjects**	**Cmax (90% CI)**	**AUC (90% CI)**	**Cmin (90%CI)**
Indinavir	800 mg q8h x 14 days	200 mg qd x 14 days	11	↔	↔	↔
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg qd x 9 days	11,12[a]	↔	↓ 16% (↓38-↑15%)	↓ 16% (↓42-↑20%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↓ 12% (↓32-↑13%)[b]	↓ 12% (↓35-↑18%)[b]	↓ 21% (↓53-↑33%)
Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)	↑ 25% (7-46%)[b]

Saquinavir SGC[c]	1200 mg q8h x 10 days	600 mg qd x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%)[b]
Tenofovir[d]	300 mg qd	600 mg qd x 14 days	30	↔	↔	↔
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↔	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	12	↑ 11% (3-19%)	↔	↔
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
Itraconazole	200 mg q12h x 14 days	600 mg qd x 28 days	16	↔	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	11	↔	↔	↓ 12% (↓ 24-↑1%)
Rifampin	600 mg x 7 days	600 mg qd x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days 300 mg po q 12h days 2-7 400 mg po q12h days 2-7	400 mg qd x 9 days 300 mg qd x 7 days 300 mg qd x 7 days	NA NA NA	↑ 38%[e] ↓ 14%[f] (7-21%) ↔[f]	↑44%[e] ↔[f] ↑ 17%[f] (6-29%)	NA NA NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↔	↔	↔
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	11	↔	↔	↔

				Efavirenz (mean % change)		
Coadministered Drug	**Dose**	**Efavirenz Dose**	**Number of**	**Cmax (90%**	**AUC (90% CI)**	**Cmin (90%**
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 12% (↓28-↑8%)	↔	↓ 12% (↓25-↑3%)
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, 400 mg qd x 15 days	600 mg qd 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↔	↔	↔
Diltiazem	240 mg x 14 days	600 mg qd 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	12	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↑ 11% (6-16%)	↔	↔

↑Indicates increase ↓ Indicates decrease ↔Indicates no change or a mean increase or decrease of <10%

[a] Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for efavirenz alone.

b 95% CI.

[C] Soft Gelatin Capsule.

[d] Tenofovir disoproxil fumarate

E 90% CI not available.

F Relative to steady-state administration of efavirenz (600 mg once daily for 9 days). NA = not available

Lamivudine

Pharmacokinetics

Pharmacokinetics in Adults: The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-l-infected adult patients after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg/kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5 mg to 600 mg/day administered to HBV-infected patients.

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 cross overstudy in 60 healthy volunteers. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma AUC24, ss; however, Cmax,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 AUC24,ss and Cmax24,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. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known. Absorption and Bioavailability: Lamivudine was rapidly absorbed after oral administration in HIV-1-infected patients. Absolute bioavailability in 12 adult patients was 86%±16% (mean ± SD) for the 150-mg tablet and 87%±13% for the oral solution. After oral administration of 2 mg/kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration (Cmax) was 1.5 ± 0.5 mcg/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/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/kg twice daily. Effects of Food on Oral Absorption: An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-1-infected patients 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; therefore, lamivudine tablets may be administered with or without food.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/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 low (<36%). In vitro studies showed that over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Metabolism: Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-l-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Elimination: 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/min (mean ± SD). In 20 HIV-l-infected patients given a single IV dose, renal clearance was 280.4 ± 75.2 mL/min (mean SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine. In most single-dose studies in HIV-1-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life (t1/2) ranged from 5 to 7 hours. In HIV-1-infected patients, total clearance was 398.5 ±69.1 mL/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/kg.

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

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

	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)	111 ± 14	28 ± 8	6 ± 2
Cmax (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC< (mcgλhr/mL)			
CL/F (mL/min)	11.0 ± 1.7	48.0 ± 19	157 ± 74
	464 ± 76	114 ± 34	36 ± 11

Exposure (AUC∞), Cmax, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as creatinine clearance

decreased. 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.

Based on a study in otherwise healthy subjects with impaired renal function, hemodialysis increased lamivudine clearance from a mean of 64 to 88 mL/min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean Lamivudine exposure after a single-dose administration. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis have negligible effects on Lamivudine clearance. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification be made after routine hemodialysis or peritoneal dialysis. It is not known whether lamivudine can be removed by continuous (24-hour) hemodialysis. The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not known.

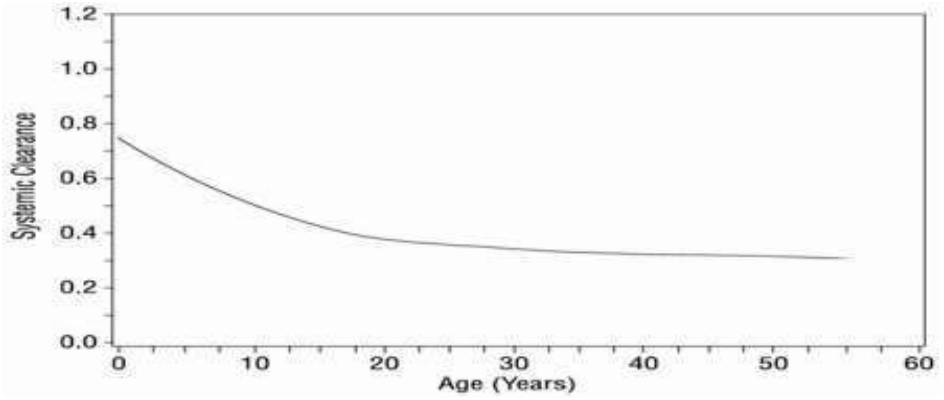
Hepatic Impairment: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Pediatric Patients: In Study NUCA2002, pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-1-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and IV administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was 66% ± 26% (mean ± SD), which was less than the 86% ± 16% (mean ± SD) observed in adults.

The mechanism for the diminished absolute bioavailabilty of lamivudine in infants and children is unknown.

Systemic clearance decreased with increasing age in pediatric patients, as shown in the below Figure.

Figure: Systemic Clearance (L/hr•kg) of Lamivudine in Relation to Age



After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age, Cmax was 1.1 ± 0.6 mcg/mL and half- life was 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8-mg/kg/day dose and adults receiving a 4-mg/kg/day dose.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours postdose. At the dose o f 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/mL.

Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants up to 1 week of age in 2 studies in South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients (>3 months of age) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age-ranges >3 months old.

Geriatric Patients: The pharmacokinetics of lamivudine after administration of lamivudine to patients over 65 years of age have not been studied.

Gender: There are no significant gender differences in lamivudine pharmacokinetics.

Race: There are no significant racial differences in lamivudine pharmacokinetics.

Drug Interactions: Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-l/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-l/HCV co-infected patients.

Trimethoprim/Sulfamethoxazole: Lamivudine and TMP/SMX were co administered to 14 HIV-1- positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose

in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC∞, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine.

Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-l-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Tenofovir disoproxil fumarate

Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted subjects is approximately 25%. Following oral administration of a single dose of tenofovir disoproxil fumarate 300 mg 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 mcg/mL and 2.29 ± 0.69 mcg· hr/mL, respectively.

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

In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 4 oz. applesauce) in healthy adult volunteers, the mean Cmax of tenofovir was 26% lower for the oral

powder relative to the tablet formulation. Mean AUC of tenofovir was similar between the oral powder and tablet formulations.

Distribution

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 mcg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism and Elimination

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes. Following IV administration of tenofovir, approximately 70 to 80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir disoproxil fumarate 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.

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.

Effects of Food on Oral Absorption

Administration of tenofovir disoproxil fumarate 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 AUC0-∞ of approximately 40% and an increase in Cmax of approximately 14%. However, administration of tenofovir disoproxil fumarate 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. Cmax and AUC of tenofovir are 0.33 ± 0.12 mcg/mL and 3.32 ± 1.37 mcg·hr/mL following multiple doses of tenofovir disoproxil fumarate 300 mg once daily in the fed state, when meal content was not controlled.

Special Populations

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

Gender: Tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric Patients 2 Years of Age and Older: Steady-state pharmacokinetics of tenofovir were evaluated in 31 HIV-1 infected pediatric subjects 2 to less than 18 years. Tenofovir exposure achieved in these

pediatric subjects receiving oral once daily doses of tenofovir disoproxil fumarate 300 mg (tablet) or 8 mg/kg of body weight (powder) up to a maximum dose of 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil fumarate 300 mg.

Table: Mean (± SD) Tenofovir Pharmacokinetic Parameters by Age Groups for Pediatric Patients

Dose and Formulation	**300 mg Tablet**
	12 to <18 Year (N=8)
C_{max} (mcg/mL)	0.38 ± 0.13
Auc_{tau} (mcg •hr/mL)	3.39 ± 1.22

Geriatric Patients: Pharmacokinetic trials have not been performed in the elderly (65 years and older).

Patients with Impaired Renal Function: 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 AUC0-∞ of tenofovir were increased. It is recommended that the dosing interval for tenofovir disoproxil fumarate be modified in patients with creatinine clearance below 50 mL/min or in patients with ESRD who require dialysis.

Table: Pharmacokinetic Parameters (Mean ± SD) of Tenofovir[a] in Subjects with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	**>80**	**50 - 80 (N=10)**	**30 - 49**	**12 - 29 (N=11)**
Cmax (mcg/mL)	0.34 ± 0.03	0.33 ± 0.06	0.37 ± 0.16	0.60 ± 0.19
$AUC_{0-\infty}$ (mcg·hr/mL)	2.18 ± 0.26	3.06 ± 0.93	6.01 ± 2.50	15.98 ± 7.22
CL/F (mL/min)	1043.7 ±	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CLrenal (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

[a] 300 mg, single dose of tenofovir disoproxil fumarate

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600 mg/300 mg/300 mg Hetero

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

Patients with Hepatic Impairment: The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate 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 disoproxil fumarate dosing is required in patients with hepatic impairment.

Assessment of Drug Interactions At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP mediated interactions involving tenofovir with other medicinal products is low.

Tenofovir disoproxil fumarate has been evaluated in healthy volunteers in combination with abacavir, atazanavir, didanosine, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir and tacrolimus. Tables 23 and 24 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug.

Table: Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[a] in the Presence of the Coadministered Drug

Coadministered Drug	**Dose of Coadministered Drug (mg)**	**N**	**% Change Of Tenofovir Pharmacokinetic Parameters[b] (90% CI)**		
			Cmax	**AUC**	**cmin**
Abacavir	300 once	8	□	□	NC
Atazanavir[c]	400 once daily x 14 days	33	↑14 (↑ 8 το ↑ 20)	↑24 (↑ 21 το ↑ 28)	↑22 (↑ 15 το ↑ 30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔

Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Entecavir	1 mg once daily x 10 days	28	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑14 (∃3 το ↑ 33)	⇔	⇔
Lamivudine	150 twice daily x7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	⇔	↑32 (↑ 25 το ↑ 38)	↑51 (↑ 37 το ↑ 66)
Nelfinavir	1250 twice daily x 14 days	29	⇔	⇔	⇔
Saquinavir/ Ritonavir	1000/100 twice daily x 14 days	35	⇔	⇔	↑23 (↑ 16 το ↑ 30)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑13 (↑1 το↑ 27)	⇔	⇔

a. Subjects received tenofovir disoproxil fumarate 300 mg once daily.

b. Increase = ↑; Decrease = ∃; No Effect =⇔; NC = Not Calculated

c. Reyataz Prescribing Information

Following multiple dosing to HIV- and HBV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady state Tenofovir pharmacokinetics were similar to those observed in previous trials, indicating lack of clinically significant drug interactions between these agents and tenofovir disoproxil fumarate.

Table: Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate

Coadministered Drug	**Dose of Coadministered Drug (mg)**	**N**	**% Change of Coadministered Drug Pharmacokinetic Parameters[a]**		
			C_{max}	**AUC**	**C_{min}**

Abacavir	300 once	8	↑12 (↓1 to ↑26)	⇔	NA
Atazanavir[b]	400 once daily x 14 days	34	↓21 (↓ 27 to ↓ 14)	↓25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[b]	Atazanavir/ Ritonavir 300/100 once daily x 42 days	10	↓28 (↓ 50 to↑5)	c (↓ 42 to ↓ 3)	c (↓ 46 to ↑ 10)
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x7 days	17	⇔	⇔	↑20 (↑ 12 to ↑29)
Entecavir	1 mg once daily x 10 days	28	⇔	↑13 (↑11 to ↑15)	⇔
Indinavir	800 three times daily x 7 days	12	↓11 (↓ 30 to ↑ 12)	⇔	⇔

Lamivudine	150 twice daily x 7 days	15	∃24 (∃34 τo ∃1 2)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔

Methadone[d]	40-110 once daily x 14 days[e]	13	⇔	⇔	⇔
Nelfinavir M8 metabolite	1250 twice daily x 14 days	29	⇔ ⇔	⇔ ⇔	⇔ ⇔
Oral Contraceptives[f]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen) once daily x 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily x 14 days	32	↑22 (↑ 6 το ↑ 41) ⇔	↑29[γ] (↑ 12 το ↑ 48) ⇔	↑47[γ] (↑ 23 το ↑ 76) ↑ 23 (↑ 3 το ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	⇔	⇔	⇔

a. Increase = ↑; Decrease = ↓; No Effect = □; NA = Not Applicable

b. Reyataz Prescribing Information

c. In HIV-infected subjects, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and Cmin values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

d. R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.

e. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.

f. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.

g. Increases in AUC and Cmin are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

Below table summarizes the drug interaction between tenofovir disoproxil fumarate and didanosine.

Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution. When administered with multiple doses of tenofovir disoproxil fumarate, the Cmax and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules were administered with tenofovir Disoproxil fumarate, systemic exposures to didanosine were similar to those seen with the 400 mg entericcoated capsules alone under fasted conditions.

Table: Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of Tenofovir Disoproxil Fumarate

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

a. Administration with food was with a light meal (~373 kcal, 20% fat).

b. Increase = ↑; Decrease = ↓; No Effect = □

c. Includes 4 subjects weighing less than 60 kg receiving ddl 250 mg.

5.3 Preclinical safety data Efavirenz:

Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays. Efavirenz induced foetal resorptions in rats. Malformations were observed in 3 of 20 foetuses/ newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma Efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, microphthalmia was observed in another foetus, and cleft palate was observed in a third foetus. No malformations were observed in foetuses from efavirenz-treated rats and rabbits. Biliary hyperplasia was observed in cynomolgus monkeys given efavirenz for 1 year at a dose resulting in mean AUC values approximately 2-fold greater than those in humans given the recommended dose. The biliary hyperplasia regressed upon cessation of dosing. Biliary fibrosis has been observed in rats. Non-sustained convulsions were observed in some monkeys receiving efavirenz for 1 year, at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose.

Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice. The mechanism of tumour formation and the potential relevance for humans are not known.

Carcinogenicity studies in male mice, male and female rats were negative. While the carcinogenic potential in humans is unknown, these data suggest that the clinical benefit of efavirenz outweighs the potential carcinogenic risk to humans.

Lamivudine:

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reductions in liver weight. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia.

Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an in vitro cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic in vivo at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the in vitro mutagenic activity of lamivudine could not be confirmed in in vivo tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment. A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that foetuses

exposed in utero to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

Tenofovir Disoproxil Fumarate:

Non-clinical safety pharmacology studies reveal no special hazard for humans. Findings in repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Croscarmellose sodium, Sodium lauryl sulfate, Hydroxy propyl cellulose, Purified Water, Anhydrous Lactose, Magnesium stearate, Pregelatinized Starch, Isopropyl Alcohol, Microcrystalline Cellulose, Sodium Starch Glycolate (Primojel) & Opadry II Yellow 85F520012 IH.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

600mg/300mg/300mg:

Container: 30s, 90s & 180s HDPE Container

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

7.1 Name and Address of Applicant

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7.2 Name and Address of Manufacturer

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