

**Hetero**

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

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**1. Name of the medicinal product**

**INN Name** : Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets  
600mg/300mg/300mg

**Proprietary Name** : Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets  
600mg/300mg/300mg

**Strength** : 600mg/300mg/300mg

**Pharmaceutical form:** film coated Tablet

**2. Qualitative and quantitative composition**

600 mg of Efavirenz, 300 mg of Lamivudine and 300mg Tenofovir Disoproxil Fumarate.

For excipients, see 6.1.

**3. Pharmaceutical form**

**Dosage form:** Tablet

**Description:** 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**

It is a fixed dose combination of emtricitabine and tenofovir disoproxil fumarate. It is indicated in antiretroviral combination therapy for the treatment of HIV 1 infected adults..

**4.2 Posology and method of administration**

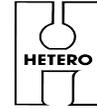
**Posology**

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 40 kg

**Recommended Dose in Adults and Pediatric Patients (weighing at least 40 kg)**

The recommended dose of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate (containing 600 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) is one tablet per day taken orally on an empty stomach, preferably at bedtime.

**.Renal impairment:** Because Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is a



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fixed-dose combination tablet, it is not recommended for patients with impaired renal function (creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis.

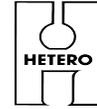
**4.3 Contraindications**

For some drugs, competition for CYP3A by efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated with Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets are listed in Table 1.

**Table 1: Drugs That are Contraindicated or Not Recommended for Use with Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets**

<b>Drug Class: Drug Name</b>	<b>Clinical Comment</b>
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylegonovine)	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 ( <i>Hypericum perforatum</i> )	May lead to loss of virologic response and possible resistance to efavirenz or to the class of non-nucleoside reverse transcriptase inhibitors (NNRTI).

**.4.4 Special warnings and special precautions for use**

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**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 lamivudine and 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 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).

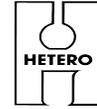
**Patients Coinfected with HIV-1 and HBV**

It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Discontinuation of anti-HBV therapy, including lamivudine and tenofovir disoproxil fumarate, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Efavirenz, Lamivudine and 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.

**Important Differences Among Lamivudine-Containing Products:**

Lamivudine Tablets contain a higher dose of the same active ingredient (lamivudine) than EPIVIR-HBV Tablets. EPIVIR-HBV 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 or tenofovir disoproxil fumarate-containing product such as VIREAD 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 subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment.



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### **Emergence of Lamivudine-Resistant HBV**

. In non-HIV-1-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 (see full prescribing information for EPIVIR-HBV for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus

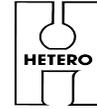
### **Coadministration with Other Products**

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is a fixed dose combination product of efavirenz, lamivudine and tenofovir disoproxil fumarate and should not be coadministered concomitantly with other efavirenz-containing, lamivudine-containing, tenofovir-containing, or emtricitabine-containing drugs, including COMBIVIR<sup>®</sup> (lamivudine/zidovudine), EPIVIR<sup>®</sup> or EPIVIR-HBV<sup>®</sup> (lamivudine), EPZICOM<sup>®</sup> (abacavir sulfate/lamivudine), TRIZIVIR<sup>®</sup> (abacavir sulfate/lamivudine/zidovudine), EMTRIVA<sup>®</sup> (emtricitabine), TRUVADA<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate), VIREAD (tenofovir disoproxil fumarate), ATRIPLA<sup>®</sup> (emtricitabine/efavirenz/tenofovir disoproxil fumarate), COMPLERA<sup>®</sup> (rilpivirine/emtricitabine/tenofovir), or STRIBILD<sup>®</sup> (elvitegravir/cobicistat/tenofovir/emtricitabine).

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should not be administered in combination with HEPSERA<sup>®</sup> (adefovir dipivoxil)

### **Use With Interferon- and Ribavirin-Based Regimens**

*In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients [see *Clinical Pharmacology (12.3)*], hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation.



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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 Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

### **New Onset or Worsening Renal Impairment**

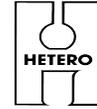
Tenofovir, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate [*See Adverse Reactions (6.2)*].

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<sup>®</sup> (adefovir dipivoxil).

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent.

### **Psychiatric Symptoms**

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. 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

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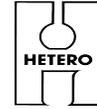
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006, treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric 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, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, 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 [see *Warnings and Precautions* (5.7)]. Dosing at bedtime may improve the tolerability of these nervous system symptoms [see *Dosage and Administration* (2.1)].

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



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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**

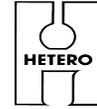
#### **. Pregnancy Category D.**

Efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, 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



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within 1 month (median duration, 16 days). 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. For patients who have had a life-threatening cutaneous reaction (eg, Stevens-Johnson syndrome), alternate therapy should be considered

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 [see *Use in Specific Populations (8.7)*]. A few of the postmarketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors [see *Adverse Reactions (6.2)*]. 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 [see *Nonclinical Toxicology (13.2)*]. 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 level

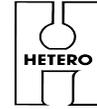
### **Lipid Elevations**

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.

### **Decreases in Bone Mineral Density**

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Module-1.5.1



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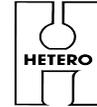
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Assessment of bone mineral density (BMD) should be considered for adults and pediatric patients 12 years of age and older who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation 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, a component of Efavirenz, Lamivudine and 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 study. 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 ( $-2.2\% \pm 3.9$ ) compared with subjects receiving stavudine + lamivudine + efavirenz ( $-1.0\% \pm 4.6$ ). Changes in BMD at the hip were similar between the two treatment groups ( $-2.8\% \pm 3.5$  in the tenofovir disoproxil fumarate group vs.  $-2.4\% \pm 4.5$  in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the study 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 N-telopeptide) 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 study of HIV-1 infected pediatric subjects 12 years of age and older (Study 321), bone effects were similar to adult subjects. Under normal circumstances BMD increases rapidly in this age group. In this study, the mean rate of bone gain was less in the tenofovir disoproxil fumarate-treated group compared to the placebo group. Six tenofovir disoproxil fumarate treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at 48 weeks. Among 28 subjects receiving 96 weeks of tenofovir disoproxil fumarate, Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil fumarate-treated



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pediatric subjects 12 years of age and older 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

### **Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including efavirenz, lamivudine and 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-Barre 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.

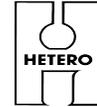
### **Fat Redistribution**

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.

### **ADVERSE REACTIONS**

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis [*See Boxed Warning, Warnings and Precautions*]
- Severe Acute Exacerbations of Hepatitis B [*See Boxed Warning, Warnings and Precautions*]
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C [*See Warnings and Precautions*]
- Pancreatitis [*See Warnings and Precautions*]
- New Onset or Worsening Renal Impairment [*See Warnings and Precautions*]



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- Psychiatric symptoms [see Warnings and Precautions
- Nervous system symptoms [see Warnings and Precautions
- Rash [see Warnings and Precautions
- Decreases in Bone Mineral Density [See Warnings and Precautions
- Immune Reconstitution Syndrome [See Warnings and Precautions .

**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.

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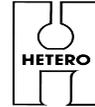
Treatment-Naïve Patients

Study 903 - Treatment-Emergent Adverse Reactions: The most common adverse reactions seen in a double-blind comparative controlled study 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 Table 2

**Table 2 Selected Treatment-Emergent Adverse Reactions<sup>a</sup> (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
<b>Body as a Whole</b>		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal pain	7%	12%
Back pain	9%	8%
Asthenia	6%	7%
<b>Digestive System</b>		
Diarrhea	11%	13%



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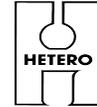
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
	<b>Tenofovir disoproxil fumarate + 3TC + EFV</b>	<b>d4T + 3TC + EFV</b>
	<b>N=299</b>	<b>N=301</b>
<b>Metabolic Disorders</b>		
Lipodystrophy <sup>b</sup>	1%	8%
<b>Musculoskeletal</b>		
Arthralgia	5%	7%
Myalgia	3%	5%
<b>Nervous System</b>		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy <sup>c</sup>	1%	5%
Anxiety	6%	6%
<b>Respiratory</b>		
Pneumonia	5%	5%
<b>Skin and Appendages</b>		
Rash event <sup>d</sup>	18%	12%

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

<sup>b</sup> Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.

<sup>c</sup> Peripheral neuropathy includes peripheral neuritis and neuropathy.

<sup>d</sup> Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.



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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 study 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 Table 3.

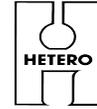
**Table 3 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Patients Randomized to Efavirenz, Lamivudine and Tenofovir disoproxil fumarate in Study 903 (0 to144 Weeks)**

	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: >845 U/L)	12%	12%
Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L; F: >170 U/L)	5%	7%
ALT (M: >215 U/L; F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophils (<750/mm <sup>3</sup> )	3%	1%
Fasting Triglycerides (>750 mg/dL)	1%	9%

**Pediatrics**

*Efavirenz*

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



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

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patients had Grade 4 rash, and five patients (9%) discontinued because of rash [see *Warnings and Precautions (5.10)*].

### *Tenofovir disoproxil fumarate*

Assessment of adverse reactions in one randomized trial (Study 321) in 87 HIV-1 infected pediatric subjects (12 to less than 18 years of age) who received treatment with VIREAD (N=45) or placebo (N=42) 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.

### **Postmarketing Experience**

The following adverse reactions have been reported during postmarketing use for each of the individual components of Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate. 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 and tenofovir DF.

#### **Efavirenz**

Body as a Whole: allergic reactions, asthenia, redistribution/accumulation of body fat [see *Warnings and Precautions (5.16)*]

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

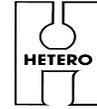
**Musculoskeletal:** arthralgia, myalgia, myopathy

**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



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### **Lamivudine**

**Body as a Whole:** Redistribution/accumulation of body fat [*see Warnings and Precautions*]

**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 [*see Boxed Warning, Warnings and Precautions (5.1, 5.2)*].

**Hypersensitivity:** Anaphylaxis, urticaria.

**Musculoskeletal:** Muscle weakness, CPK elevation, rhabdomyolysis.

**Skin:** Alopecia, pruritus.

### **Tenofovir Disoproxil Fumarate**

**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

**Renal and Urinary Disorders:** Renal insufficiency, 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 [*see Warnings and Precautions (5.6)*].

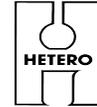
**Hepatobiliary Disorders:** Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

**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

**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,



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muscular weakness, myopathy, hypophosphatemia.

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

**DRUG INTERACTIONS**

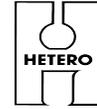
No drug interaction studies have been conducted using Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. However, drug interaction studies have been conducted with the individual components efavirenz, lamivudine and tenofovir disoproxil fumarate [see *Clinical Pharmacology (12.3)*].

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

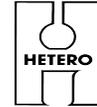
Drugs that induce CYP3A activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with efavirenz are summarized in Tables 1 and 4 [for pharmacokinetics data see *Clinical Pharmacology (12.3, Tables 5 and 6)*]. The tables include potentially significant interactions, but are not all inclusive.

<b>Table 4: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction</b>		
<b>Concomitant Drug Class: Drug Name</b>	<b>Effect</b>	<b>Clinical Comment</b>
<i>HIV</i> <i>antiviral</i> <i>agents</i>		
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir	Fosamprenavir (unboosted): Appropriate doses of the combinations with respect to safety and efficacy have not been established.  Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with



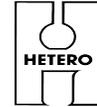
**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg**

		fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir*	<i>Treatment-naïve patients:</i> 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). <i>Treatment-experienced patients:</i> Coadministration 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 C <sub>min</sub> 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.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir*	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



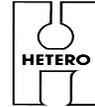
**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg**

		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	↑ ritonavir* ↑ efavirenz*	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.
<b>Concomitant Drug Class: Drug Name</b>	<b>Effect</b>	<b>Clinical Comment</b>
Protease inhibitor: Saquinavir	↓ saquinavir*	Should not be used as sole protease inhibitor in combination with efavirenz.
NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. Efavirenz should not be coadministered with other NNRTIs.
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc*	Refer to the full prescribing information for maraviroc for guidance on Coadministration with efavirenz.
Integrase strand transfer inhibitor: Raltegravir	↓ raltegravir*	Efavirenz reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.
<i>Hepatitis C antiviral agents</i>		
Protease inhibitor: boceprevir	↓ boceprevir*	Plasma trough concentrations of boceprevir were decreased when boceprevir was coadministered with efavirenz, which may result in loss of therapeutic effect. The combination should be avoided.



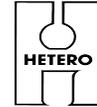
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Protease inhibitor: Telaprevir	↓ telaprevir* ↓ efavirenz*	Concomitant administration of telaprevir and efavirenz resulted in reduced steady-state exposures to telaprevir and efavirenz.
<i>Other agents</i>		
Anticoagulant: Warfarin	↑ or ↓ warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine* ↓ efavirenz*	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants: Bupropion  Sertraline	↓ bupropion* ↓ sertraline*	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*	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



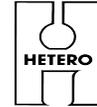
**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg**

		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. [ <i>Clinical Pharmacology (12.3, Tables 5 and 6).</i> ]
Itraconazole	↓ itraconazole* ↓	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment
Ketoconazole	↓ ketoconazole	Drug interaction studies with efavirenz and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.



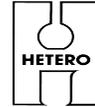
**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg**

<b>Concomitant Drug Class: Drug Name</b>	<b>Effect</b>	<b>Clinical Comment</b>
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 (see <i>Other Drugs</i> , following table). 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 *	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, 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



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		channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin* ↓ pravastatin* ↓ simvastatin*	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgestimate  Implant Etonogestrel	↓ active metabolites of norgestimate*  ↓ etonogestrel	A reliable method of barrier contraception 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.
<b>Concomitant Drug Class: Drug Name</b>	<b>Effect</b>	<b>Clinical Comment</b>
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



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

**Other Drugs**

Based on the results of drug interaction studies [see *Clinical Pharmacology (12.3, Tables 5 and 6)*], 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.

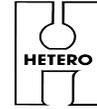
**Cannabinoid Test Interaction**

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

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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-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin

**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

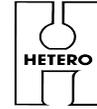
**Tenofovir Disoproxil Fumarate****Didanosine**

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

When administered with tenofovir disoproxil fumarate, the  $C_{max}$  and AUC of didanosine (administered as either the buffered or enteric-coated formulation) increased significantly [*See Clinical Pharmacology (12.3)*]. 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 DF. Data are not available to recommend a dose adjustment of didanosine for adults or pediatric patients weighing less than 60 kg. When coadministered, tenofovir disoproxil fumarate and didanosine enteric coated capsule 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**

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Atazanavir has been shown to increase tenofovir concentrations [See *Clinical Pharmacology (12.3)*]. 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  $C_{min}$  of atazanavir [See *Clinical Pharmacology (12.3)*]. When coadministered with tenofovir 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 [See *Clinical Pharmacology (12.3)*]. 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 fumarate-associated adverse reactions.

**Drugs Affecting Renal Function**

Since tenofovir is primarily eliminated by the kidneys [See *Clinical Pharmacology (12.3)*], 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, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

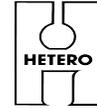
In the treatment of chronic hepatitis B, tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (adefovir dipivoxil).

**4.6 Pregnancy and lactation****Pregnancy:**

Pregnancy Category D:

**. Efavirenz:**

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

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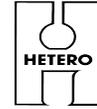
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reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic 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 in these three monkey fetuses included anencephaly and unilateral anophthalmia in one fetus, microphthalmia 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

**Lamivudine:**

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



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

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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 embryoletality 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

### **Tenofovir Disoproxil Fumarate:**

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

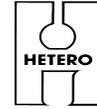
### **Animal Data**

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.

### **Nursing Mothers**

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV-1 transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving Efavirenz, Lamivudine and Tenofovir disoproxil fumarate.

**Efavirenz:** Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats.



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

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**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.

*Tenofovir Disoproxil Fumarate:* 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.

### **Pediatric Use**

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets should only be administered to pediatric patients with a body weight greater than or equal to 40 kg (greater than or equal to 88 lbs).

### **Geriatric Use**

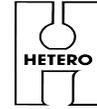
Clinical studies of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater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

### **Patients with impaired renal function**

Lamivudine and tenofovir disoproxil fumarate tablets are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because they are part of a fixed-dose combination formulation that cannot be adjusted.

### **Hepatic Impairment**

Efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, 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



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

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### **4.9 Overdose**

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

**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 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. 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.

**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.

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**

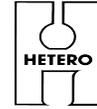
### **EFAVIRENZ**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitors. ATC code: J05AG03

#### Mechanism of action

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

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Efavirenz is a NNRTI of HIV-1. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) and does not significantly inhibit HIV-2 RT or cellular DNA polymerases ( $\alpha$ ,  $\beta$ ,  $\gamma$  or  $\delta$ ).

### Antiviral activity

The free concentration of efavirenz required for 90 to 95% inhibition of wild type or zidovudine-resistant laboratory and clinical isolates *in vitro* ranged from 0.46 to 6.8 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures.

### Resistance

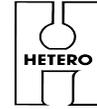
The potency of efavirenz in cell culture against viral variants with amino acid substitutions at positions 48, 108, 179, 181 or 236 in RT or variants with amino acid substitutions in the protease was similar to that observed against wild type viral strains. The single substitutions which led to the highest resistance to efavirenz in cell culture correspond to a leucine-to-isoleucine change at position 100 (L100I, 17 to 22-fold resistance) and a lysine-to-asparagine at position 103 (K103N, 18 to 33-fold resistance). Greater than 100-fold loss of susceptibility was observed against HIV variants expressing K103N in addition to other amino acid substitutions in RT.

K103N was the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during clinical studies of efavirenz in combination with indinavir or zidovudine + lamivudine. This mutation was observed in 90% of patients receiving efavirenz with virological failure. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. The pattern of amino acid substitutions in RT associated with resistance to efavirenz was independent of the other antiviral medicines used in combination with efavirenz.

### Cross resistance

Cross resistance profiles for efavirenz, nevirapine and delavirdine in cell culture demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs. Two of three delavirdine-resistant clinical isolates examined were cross-resistant to efavirenz and contained the K103N substitution. A third isolate which carried a substitution at position 236 of RT was not cross-resistant to efavirenz.

Viral isolates recovered from PBMCs of patients enrolled in efavirenz clinical studies who showed evidence of treatment failure (viral load rebound) were assessed for susceptibility to



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

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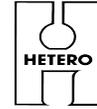
NNRTIs. Thirteen isolates previously characterised as efavirenz-resistant were also resistant to nevirapine and delavirdine. Five of these NNRTI-resistant isolates were found to have K103N or a valine-to-isoleucine substitution at position 108 (V108I) in RT. Three of the efavirenz treatment failure isolates tested remained sensitive to efavirenz in cell culture and were also sensitive to nevirapine and delavirdine.

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

### Clinical efficacy

Efavirenz has not been studied in controlled studies in patients with advanced HIV disease, namely with CD4 counts < 50 cells/mm<sup>3</sup>, or in PI or NNRTI experienced patients. Clinical experience in controlled studies with combinations including didanosine or zalcitabine is limited. Two controlled studies (006 and ACTG 364) of approximately one year duration with efavirenz in combination with NRTIs and/or PIs, have demonstrated reduction of viral load below the limit of quantification of the assay and increased CD4 lymphocytes in antiretroviral therapy-naïve and NRTI-experienced HIV-infected patients. Study 020 showed similar activity in NRTI-experienced patients over 24 weeks. In these studies the dose of efavirenz was 600 mg once daily; the dose of indinavir was 1,000 mg every 8 hours when used with efavirenz and 800 mg every 8 hours when used without efavirenz. The dose of nelfinavir was 750 mg given three times a day. The standard doses of NRTIs given every 12 hours were used in each of these studies.

Study 006, a randomized, open-label trial, compared efavirenz + zidovudine + lamivudine or efavirenz + indinavir with indinavir + zidovudine + lamivudine in 1,266 patients who were required to be efavirenz-, lamivudine-, NNRTI-, and PI-naïve at study entry. The mean baseline CD4 cell count was 341 cells/mm<sup>3</sup> and the mean baseline HIV-RNA level was 60,250 copies/ml. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 3. In the analysis of responder rates (the non-completer equals failure analysis [NC = F]), patients who terminated the study early for any reason, or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit of assay quantification were considered to have HIV-RNA above 50 or above 400 copies/ml at the missing time points.



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

**Table 3: Efficacy results for study 006**

		Responder rates (NC = F <sup>a</sup> ) Plasma HIV-RNA		Mean change from baseline- CD4 cell count
		< 400 copies/ml (95% C.I. <sup>b</sup> )	< 50 copies/ml (95% C.I. <sup>b</sup> )	cells/mm <sup>3</sup> (S.E.M. <sup>c</sup> )
Treatment Regimen <sup>d</sup>	n	48 weeks	48 weeks	48 weeks
EFV + ZDV + 3TC	202	67% (60%, 73%)	62% (55%, 69%)	187 (11.8)
EFV + IDV	206	54% (47%, 61%)	48% (41%, 55%)	177 (11.3)
IDV + ZDV + 3TC	206	45% (38%, 52%)	40% (34%, 47%)	153 (12.3)

<sup>a</sup> NC = F, noncompleter = failure.

<sup>b</sup> C.I., confidence interval.

<sup>c</sup> S.E.M., standard error of the mean.

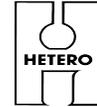
<sup>d</sup> EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir.

Long-term results at 168 weeks of study 006 (160 patients completed study on treatment with EFV+IDV, 196 patients with EFV+ZDV+3TC and 127 patients with IDV+ZDV+3TC, respectively), suggest durability of response in terms of proportions of patients with HIV RNA < 400 copies/ml, HIV RNA < 50 copies/ml and in terms of mean change from baseline CD4 cell count.

Efficacy results for studies ACTG 364 and 020 are found in Table 4. Study ACTG 364 enrolled 196 patients who had been treated with NRTIs but not with PIs or NNRTIs. Study 020 enrolled 327 patients who had been treated with NRTIs but not with PIs or NNRTIs. Physicians were allowed to change their patient's NRTI regimen upon entry into the study. Responder rates were highest in patients who switched NRTIs

**Table 4: Efficacy results for studies ACTG 364 and 020**

		Responder rates (NC = F <sup>a</sup> ) Plasma HIV-RNA				Mean change from baseline-CD4 cell count	
Study	Number/ Treatment Regimens <sup>b</sup>	n	% (95% C.I. <sup>c</sup> )	% (95% C.I.)	cells/mm <sup>3</sup>	(S.E.M. <sup>d</sup> )	
Study ACTG 364			< 500 copies/ml	< 50 copies/ml			
48 weeks							
EFV + NFV + NRTIs		65	70 (59, 82)	---	107	(17.9)	

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

EFV + NRTIs	65	58	(46, 70)	---	---	114	(21.0)
NFV + NRTIs	66	30	(19, 42)	---	---	94	(13.6)
Study 020 24 weeks		< 400 copies/ml		< 50 copies/ml			
EFV + IDV + NRTIs	157	60	(52, 68)	49	(41, 58)	104	(9.1)
IDV + NRTIs	170	51	(43, 59)	38	(30, 45)	77	(9.9)

<sup>a</sup> NC = F, noncompleter = failure.

<sup>b</sup> EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir; NRTI, nucleoside reverse transcriptase inhibitor; NFV, nelfinavir.

<sup>c</sup> C.I., confidence interval for proportion of patients in response.

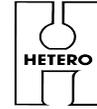
<sup>d</sup> S.E.M., standard error of the mean.

---, not performed.

Paediatric population

Study AI266922 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with didanosine and emtricitabine in antiretroviral-naïve and -experienced paediatric patients. Thirty-seven patients 3 months to 6 years of age (median 0.7 years) were treated with SUSTIVA. At baseline, median plasma HIV-1 RNA was 5.88 log<sub>10</sub> copies/mL, median CD4+ cell count was 1144 cells/mm<sup>3</sup>, and median CD4+ percentage was 25%. The median time on study therapy was 132 weeks; 27% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (21/37) and 46% (17/37), respectively. The median increase from baseline in CD4+ count at 48 weeks was 215 cells/mm<sup>3</sup> and the median increase in CD4+ percentage was 6%.

Study PACTG 1021 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with didanosine and emtricitabine in paediatric patients who were antiretroviral therapy naïve. Forty-three patients 3 months to 21 years of age (median 9.6 years) were dosed with SUSTIVA. At baseline, median plasma HIV-1 RNA was 4.8 log<sub>10</sub> copies/mL, median CD4+ cell count was 367 cells/mm<sup>3</sup>, and median CD4+ percentage was 18%. The median time on study therapy was 181 weeks; 16% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 77% (33/43) and 70% (30/43), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 238 cells/mm<sup>3</sup> and the median increase in CD4+ percentage was 13%.



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Study PACTG 382 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with nelfinavir and an NRTI in antiretroviral-naïve and NRTI-experienced paediatric patients. One hundred two patients 3 months to 16 years of age (median 5.7 years) were treated with SUSTIVA. Eighty-seven percent of patients had received prior antiretroviral therapy. At baseline, median plasma HIV-1 RNA was 4.57 log<sub>10</sub> copies/mL, median CD4+ cell count was 755 cells/mm<sup>3</sup>, and median CD4+ percentage was 30%. The median time on study therapy was 118 weeks; 25% of patients discontinued before Week 48. Using an ITT analysis, the overall proportion of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (58/102) and 43% (44/102), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 128 cells/mm<sup>3</sup> and the median increase in CD4+ percentage was 5%.

### **LAMIVUDINE**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: nucleoside analogue, ATC Code: J05AF05.

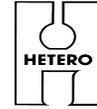
##### Mechanism of action

Lamivudine is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'-triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*, it is also active against zidovudine-resistant clinical isolates of HIV. No antagonistic effects *in vitro* were seen with lamivudine and other anti retrovirals (tested agents: abacavir, didanosine, nevirapine and zidovudine).

##### Resistance

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

*In vitro* data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite



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

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the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTI's should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTI's are available.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according to methodological factors.

Lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*.

### Clinical efficacy and safety

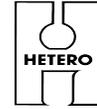
In clinical trials, lamivudine in combination with zidovudine has been shown to reduce HIV-1 viral load and increase CD4 cell count. Clinical end-point data indicate that lamivudine in combination with zidovudine, results in a significant reduction in the risk of disease progression and mortality.

Evidence from clinical studies shows that lamivudine plus zidovudine delays the emergence of zidovudine resistant isolates in individuals with no prior antiretroviral therapy.

Lamivudine has been widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (NRTIs) or different classes (PIs, non-nucleoside reverse transcriptase inhibitors).

Clinical trial evidence from paediatric patients receiving lamivudine with other antiretroviral drugs (abacavir, nevirapine/efavirenz or zidovudine) has shown that the resistance profile observed in paediatric patients is similar to that observed in adults, in terms of the genotypic substitutions detected and their relative frequency.

Children receiving lamivudine oral solution concomitantly with other antiretroviral oral solutions



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

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in clinical trials developed viral resistance more frequently than children receiving tablets (see the description of the clinical experience in paediatric population (ARROW study) and section 5.2).

Multiple drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretrovirally-naïve patients as well as in patients presenting with viruses containing the M184V mutations.

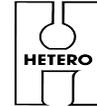
The relationship between *in vitro* susceptibility of HIV to lamivudine and clinical response to lamivudine-containing therapy remains under investigation.

Lamivudine at a dose of 100 mg once daily has also been shown to be effective for the treatment of adult patients with chronic HBV infection (for details of clinical studies, see the prescribing information for Zeffix). However, for the treatment of HIV infection only a 300 mg daily dose of lamivudine (in combination with other antiretroviral agents) has been shown to be efficacious.

Lamivudine has not been specifically investigated in HIV patients co-infected with HBV.

*Once daily dosing (300 mg once a day):* a clinical study has demonstrated the non inferiority between Efavirenz once a day and Efavirenz twice a day containing regimens. These results were obtained in an antiretroviral naïve-population, primarily consisting of asymptomatic HIV infected patients (CDC stage A).

*Paediatric population:* a randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. Of note, from this study clinical data were not available for children under one year old. The results are summarised in the table below:



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

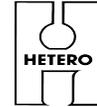
**Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)**

	<b>Twice Daily N (%)</b>	<b>Once Daily N (%)</b>
<b>Week 0 (After ≥36 Weeks on Treatment)</b>		
Plasma HIV-1 RNA <80 c/ml	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
<b>Week 48</b>		
Plasma HIV-1 RNA <80 c/ml	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
<b>Week 96</b>		
Plasma HIV-1 RNA <80 c/ml	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

In a pharmacokinetic study (PENTA 15), four virologically controlled subjects less than 12 months of age switched from abacavir plus lamivudine oral solution twice daily to a once daily regimen. Three subjects had undetectable viral load and one had plasmatic HIV-RNA of 900 copies/ml at Week 48. No safety concerns were observed in these subjects.

The abacavir + lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/ml at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200c/ml, <400c/ml, <1000c/ml), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

At the time of randomization to once daily vs twice daily dosing (Week 0), those patients who had received tablet formulations had a higher rate of viral load suppression than those who had received any solution formulations at any time. These differences were observed in each different age group studied. This difference in suppression rates between tablets and solutions remained through Week 96 with once daily dosing.



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**Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/ml: Subgroup Analysis by Formulation**

	Twice Daily Plasma HIV-1 RNA <80 c/ml: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/ml: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Any solution regimen at any time	14/26 (54)	15/30 (50)
All tablet based regimen throughouts	236/305 (77)	222/305 (73)
Week 96		
Any solution regimen at any time	13/26 (50)	17/30 (57)
All tablet based regimen throughouts	221/300 (74)	213/301 (71)

Genotypic resistance analyses were conducted on samples with plasma HIV-1 RNA >1000 copies/ml. More cases of resistance were detected among patients who had received lamivudine solution, in combination with other antiretroviral solutions, compared with those who received similar doses of tablet formulation. This is consistent with the lower rates of antiviral suppression observed in these patients.

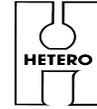
**TENOFOVIR**

**5.1 Pharmacodynamic properties**

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

Mechanism of action and pharmacodynamic effects

Tenofovir disoproxil fumarate is the fumarate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits HIV-1 reverse transcriptase and the HBV polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases  $\alpha$ ,  $\beta$ , and  $\gamma$ . At



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concentrations of up to 300 µmol/l, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in *in vitro* assays.

### *Data pertaining to HIV*

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

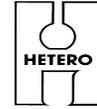
*Resistance:* Strains of HIV-1 with reduced susceptibility to tenofovir and a K65R mutation in reverse transcriptase have been selected *in vitro* and in some patients (see Clinical efficacy and safety). Tenofovir disoproxil fumarate should be avoided in antiretroviral-experienced patients with strains harbouring the K65R mutation (see section 4.4). In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir.

Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir disoproxil 245 mg (as fumarate) against strains of HIV-1 with resistance to nucleoside inhibitors. The results indicate that patients whose HIV expressed 3 or more thymidine-analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced response to tenofovir disoproxil 245 mg (as fumarate) therapy.

### Clinical efficacy and safety

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

In study GS-99-907, 550 treatment-experienced adult patients were treated with placebo or tenofovir disoproxil 245 mg (as fumarate) for 24 weeks. The mean baseline CD4 cell count was 427 cells/mm<sup>3</sup>, the mean baseline plasma HIV-1 RNA was 3.4 log<sub>10</sub> copies/ml (78% of patients had a viral load of < 5,000 copies/ml) and the mean duration of prior HIV treatment was 5.4 years. Baseline genotypic analysis of HIV isolates from 253 patients revealed that 94% of patients had HIV-1 resistance mutations associated with nucleoside reverse transcriptase inhibitors, 58% had mutations associated with protease inhibitors and 48% had mutations associated with non-nucleoside reverse transcriptase inhibitors.



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

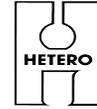
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At week 24 the time-weighted average change from baseline in  $\log_{10}$  plasma HIV-1 RNA levels (DAVG<sub>24</sub>) was -0.03  $\log_{10}$  copies/ml and -0.61  $\log_{10}$  copies/ml for the placebo and tenofovir disoproxil 245 mg (as fumarate)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

The 144-week, double-blind, active controlled phase of study GS-99-903 evaluated the efficacy and safety of tenofovir disoproxil 245 mg (as fumarate) *versus* stavudine when used in combination with lamivudine and efavirenz in HIV-1 infected adult patients naïve to antiretroviral therapy. The mean baseline CD4 cell count was 279 cells/mm<sup>3</sup>, the mean baseline plasma HIV-1 RNA was 4.91  $\log_{10}$  copies/ml, 19% of patients had symptomatic HIV-1 infection and 18% had AIDS. Patients were stratified by baseline HIV-1 RNA and CD4 count. Forty-three percent of patients had baseline viral loads > 100,000 copies/ml and 39% had CD4 cell counts < 200 cells/ml.

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

The average change from baseline for HIV-1 RNA and CD4 count at 48 weeks of treatment was similar in both treatment groups (-3.09 and -3.09  $\log_{10}$  copies/ml; +169 and 167 cells/mm<sup>3</sup> in the tenofovir disoproxil 245 mg (as fumarate) and stavudine groups, respectively). At 144 weeks of treatment, the average change from baseline remained similar in both treatment groups (-3.07 and -3.03  $\log_{10}$  copies/ml; +263 and +283 cells/mm<sup>3</sup> in the tenofovir disoproxil 245 mg (as fumarate) and stavudine groups, respectively). A consistent response to treatment with tenofovir



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disoproxil 245 mg (as fumarate) was seen regardless of baseline HIV-1 RNA and CD4 count.

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

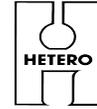
### *Data pertaining to HBV*

The antiviral activity of tenofovir disoproxil fumarate against hepatitis B virus (HBV) has been demonstrated *in vitro* and clinically in adults and adolescents. Please refer to the Summaries of Product Characteristics for Viread 245 mg film-coated tablets and Viread 33 mg/g granules.

### Paediatric population

In study GS-US-104-0321, 87 HIV-1 infected treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. Due to limitations of the study, a benefit of tenofovir disoproxil fumarate over placebo was not demonstrated based on plasma HIV-1 RNA levels at week 24. However, a benefit is expected for the adolescent population based on extrapolation of adult data and comparative pharmacokinetic data (see section 5.2).

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

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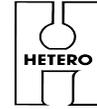
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In study GS-US-104-0352, 97 treatment-experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil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

Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil fumarate, or stavudine or zidovudine, mean lumbar spine BMD Z-score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil fumarate and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil fumarate treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil fumarate treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil fumarate treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. BMD Z-scores were not adjusted for height and weight.

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

The European Medicines Agency has deferred the obligation to submit the results of studies with Viread in one or more subsets of the paediatric population in HIV and chronic hepatitis B (see section 4.2 for information on paediatric use).



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

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### **5.2 Pharmacokinetic properties**

#### **Mechanism of Action**

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets are a fixed dose combination of antiviral drugs efavirenz, lamivudine and tenofovir disoproxil fumarate [see *Microbiology (12.4)*].

#### **Pharmacokinetics**

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets (600 mg, 300 mg, 300 mg) were bioequivalent to Sustiva<sup>®</sup> (efavirenz, 600 mg tablet), Epivir<sup>®</sup> (lamivudine 300 mg tablet) plus Viread<sup>®</sup> (tenofovir disoproxil fumarate tablet) when single doses were administered to healthy volunteers under fasting conditions.

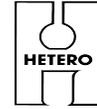
Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets (600 mg, 300 mg, 300 mg) have not been evaluated under fed conditions. Efavirenz and products containing efavirenz should be administered under fasted conditions.

#### **Efavirenz:**

In HIV-1 infected subjects 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 HIV-1 infected subjects receiving efavirenz 600 mg once daily, steady-state  $C_{max}$  was  $12.9 \pm 3.7 \mu\text{M}$  (mean  $\pm$  SD),  $C_{min}$  was  $5.6 \pm 3.2 \mu\text{M}$ , and AUC was  $184 \pm 73 \mu\text{M}\cdot\text{hr}$ . Efavirenz is highly bound (approximately 99.5 to 99.75%) to human plasma proteins, predominantly albumin. Following administration of <sup>14</sup>C-labeled efavirenz, 14 to 34% of the dose was recovered in the urine (mostly as metabolites) and 16 to 61% was recovered in feces (mostly as parent drug). *In vitro* studies suggest CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses.

#### **Lamivudine:**

After oral administration of 2 mg/kg of lamivudine twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration ( $C_{max}$ ) was  $1.5 \pm 0.5 \text{ mcg/mL}$  (mean  $\pm$  SD). The area under the plasma concentration versus time curve (AUC) and  $C_{max}$  increased in proportion to oral dose over the range from 0.25 to 10 mg/kg and absolute bioavailability in 12 adult patients was  $86\% \pm 16\%$  (mean  $\pm$  SD) for the 150-mg tablet and  $87\% \pm 13\%$  for the oral solution. Binding of lamivudine to human plasma proteins is low (<36%). Within 12 hours after a single oral dose of lamivudine in 6 HIV-1-infected adults,  $5.2\% \pm 1.4\%$  (mean  $\pm$  SD) of the dose was excreted as the trans-

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sulfoxide metabolite in the urine. The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion and the observed mean elimination half-life ( $t_{1/2}$ ) ranged from 5 to 7 hours in most single-dose studies with serum sampling for 24 hours after dosing.

**Tenofovir disoproxil fumarate:**

Following oral administration of a single 300 mg dose of tenofovir DF to HIV-1 infected subjects in the fasted state, maximum serum concentrations ( $C_{max}$ ) were achieved in  $1.0 \pm 0.4$  hrs (mean  $\pm$  SD) and  $C_{max}$  and AUC values were  $296 \pm 90$  ng/mL and  $2287 \pm 685$  ng•hr/mL, respectively. The oral bioavailability of tenofovir from tenofovir DF in fasted subjects is approximately 25%. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.01 to 25 mcg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of  $243 \pm 33$  mL/min (mean  $\pm$  SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

***Special Populations******Race***

**Efavirenz and Lamivudine:** There are no significant racial differences in efavirenz and lamivudine pharmacokinetics.

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

**Gender:**

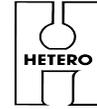
There are no significant gender differences in the pharmacokinetics of Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate.

**Geriatric Patients:**

The pharmacokinetics of lamivudine and tenofovir disoproxil fumarate have not been studied in patients over 65 years of age.

**Pediatrics:**

This combination tablet should not be administered to pediatric patients weighing less than 40



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

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Kg.

Patients with Impaired Renal Function: *See Use in Specific Populations (8.6).*

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because it is a fixed-dose combination formulation that cannot be adjusted.

Patients with Hepatic Impairment

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

**Lamivudine:** The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; 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 decompensate liver disease.

**Tenofovir disoproxil fumarate:** 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: *See Drug Interactions (7).*

### **Efavirenz:**

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  $K_i$  values (8.5 to 17  $\mu\text{M}$ ) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 ( $K_i$  values 82 to 160  $\mu\text{M}$ ) 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. Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A isozymes may result in altered plasma concentrations of the coadministered 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

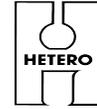


**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg**

of coadministration of efavirenz on the  $C_{max}$ , AUC, and  $C_{min}$  are summarized in Table 5 (effect of efavirenz on other drugs) and Table 6 (effect of other drugs on efavirenz). For information regarding clinical recommendations

**Table 5: Effect of Efavirenz on Coadministered Drug Plasma  $C_{max}$ , AUC, and  $C_{min}$**

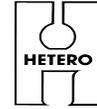
Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				$C_{max}$ (90% CI)	AUC (90% CI)	$C_{min}$ (90% CI)
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓ 59% (49-67%)	↓ 74% (68-78%)	↓ 93% (90-95%)
	400 mg qd d 1-6, then 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% <sup>a</sup> (↓ 17-↑ 58%)	↑ 39% <sup>a</sup> (2-88%)	↑ 48% <sup>a</sup> (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			



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**Table 5: Effect of Efavirenz on Coadministered Drug Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

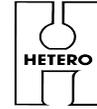
Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
	After morning dose			↔ <sup>b</sup>	↓ 33% <sup>b</sup> (26-39%)	↓ 39% <sup>b</sup> (24-51%)
	After afternoon dose			↔ <sup>b</sup>	↓ 37% <sup>b</sup> (26-46%)	↓ 52% <sup>b</sup> (47-57%)
	After evening dose			↓ 29% <sup>b</sup> (11-43%)	↓ 46% <sup>b</sup> (37-54%)	↓ 57% <sup>b</sup> (50-63%)
Lopinavir/ritonavir	400/100 mg capsule q12h x 9 days	600 mg qd x 9 days	11,7 <sup>c</sup>	↔ <sup>d</sup>	↓ 19% <sup>d</sup> (↓ 36-↑ 3%)	↓ 39% <sup>d</sup> (3-62%)
	600/150 mg tablet q12h x 10 days with efavirenz compared to 400/100 mg q12h alone	600 mg qd x 9 days	23	↑ 36% <sup>d</sup> (28-44%)	↑ 36% <sup>d</sup> (28-44%)	↑ 32% <sup>d</sup> (21-44%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↑ 21% (10-33%)	↑ 20% (8-34%)	↔
Metabolite AG-1402				↓ 40% (30-48%)	↓ 37% (25-48%)	↓ 43% (21-59%)
Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	11			
	After AM dose			↑ 24% (12-38%)	↑ 18% (6-33%)	↑ 42% (9-86%) <sup>e</sup>



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

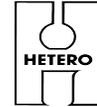
**Table 5: Effect of Efavirenz on Coadministered Drug Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
	After PM dose			↔	↔	↑ 24% (3-50%) <sup>c</sup>
Saquinavir SGC <sup>f</sup>	1200 mg q8h x 10 days	600 mg qd x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%) <sup>e</sup>
Lamivudine	150 mg q12h x 14 days	600 mg qd x 14 days	9	↔	↔	↑ 265% (37-873%)
Tenofovir <sup>g</sup>	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%)
Raltegravir	400 mg single dose	600 mg qd	9	↓ 36% (2-59%)	↓ 36% (20-48%)	↓ 21% (↓ 51-↑ 28%)
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↓ 8% (↓ 22-↑ 8%)	↓ 19% (11-25%)	↓ 44% (26-58%)
Telaprevir	750 mg q8h x 10 days	600 mg qd x 20 days	21	↓ 9% (↓ 18-↑ 2%)	↓ 26% (16-35%)	↓ 47% (35-56%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↑ 22% (4-42%)	↔	NA

**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg****Table 5: Effect of Efavirenz on Coadministered Drug Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
Clarithromycin 14-OH metabolite	500 mg q12h x 7 days	400 mg qd x 7 days	11	↓ 26%	↓ 39%	↓ 53%
				(15-35%)	(30-46%)	(42-63%)
				↑ 49%	↑ 34%	↑ 26%
				(32-69%)	(18-53%)	(9-45%)
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↔	↔
Itraconazole Hydroxy-itraconazole	200 mg q12h x 28 days	600 mg qd x 14 days	18	↓ 37%	↓ 39%	↓ 44%
				(20-51%)	(21-53%)	(27-58%)
				↓ 35%	↓ 37%	↓ 43%
				(12-52%)	(14-55%)	(18-60%)
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg qd x 10 and 20 days	11	↓ 45%	↓ 50%	NA
				(34-53%)	(40-57%)	
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	9	↓ 32%	↓ 38%	↓ 45%
				(15-46%)	(28-47%)	(31-56%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↓ 61% <sup>h</sup>	↓ 77% <sup>h</sup>	NA
	300 mg po	300 mg qd x	NA	↓ 36% <sup>i</sup>	↓ 55% <sup>i</sup>	NA

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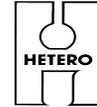


**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg**

**Table 5: Effect of Efavirenz on Coadministered Drug Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
	q12h days 2-7	7 days		(21-49%)	(45-62%)	
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↑ 23% <sup>i</sup> (↓ 1-↑ 53%)	↓ 7% <sup>i</sup> (↓ 23-↑ 13%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↓ 14% (1-26%)	↓ 43% (34-50%)	↓ 69% (49-81%)
Total active (including metabolites)				↓ 15% (2-26%)	↓ 32% (21-41%)	↓ 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	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 72% (63-79%)	↓ 68% (62-73%)	↓ 45% (20-62%)
Total active (including metabolites)				↓ 68% (55-78%)	↓ 60% (52-68%)	NA <sup>j</sup>
Carbamazepine	200 mg qd x 3 days, bid x 3 days,	600 mg qd x 14 days	12	↓ 20% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)

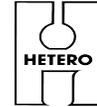
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**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg**

**Table 5: Effect of Efavirenz on Coadministered Drug Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
Epoxide metabolite	then 400 mg qd x 29 days			↔	↔	↓ 13% (↓ 30-↑ 7%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↓ 24% (18-30%)	↔	NA
Diltiazem	240 mg x 21 days	600 mg qd x 14 days	13	↓ 60% (50-68%)	↓ 69% (55-79%)	↓ 63% (44-75%)
Desacetyl diltiazem				↓ 64% (57-69%)	↓ 75% (59-84%)	↓ 62% (44-75%)
N-monodesmethyl 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				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromine			21	↓ 46% (39-52%)	↓ 64% (62-67%)	↓ 82% (79-85%)



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

**Table 5: Effect of Efavirenz on Coadministered Drug Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

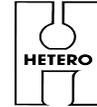
Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
Levonorgestrel			6	↓ 80% (77-83%)	↓ 83% (79-87%)	↓ 86% (80-90%)
Lorazepam	2 mg single dose	600 mg qd x 10 days	12	↑ 16% (2-32%)	↔	NA
Methadone	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 dose (sustained-release)	600 mg qd x 14 days	13	↓ 34% (21-47%)	↓ 55% (48-62%)	NA
Hydroxybupropion				↑ 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%.

<sup>a</sup> Compared with atazanavir 400 mg qd alone.

<sup>b</sup> Comparator dose of indinavir was 800 mg q8h x 10 days.

<sup>c</sup> Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for lopinavir/ritonavir alone.



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

<sup>d</sup> Values are for lopinavir; the pharmacokinetics of ritonavir in this study were unaffected by concurrent efavirenz.

<sup>e</sup> 95% CI.

<sup>f</sup> Soft Gelatin Capsule.

<sup>g</sup> Tenofovir disoproxil fumarate.

<sup>h</sup> 90% CI not available.

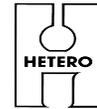
<sup>i</sup> Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).

<sup>j</sup> Not available because of insufficient data.

NA = not available.

**Table 6: Effect of Coadministered Drug on Efavirenz Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

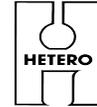
Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
Indinavir	800 mg q8h x 14 days	200 mg qd x 14 days	11	↔	↔	↔
Lopinavir/ritonavir	400/100 mg q12h x 9 days	600 mg qd x 9 days	11,12 <sup>a</sup>	↔	↓ 16% (↓ 38-↑ 15%)	↓ 16% (↓ 42-↑ 20%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↓ 12% (↓ 32-↑ 13%) <sup>b</sup>	↓ 12% (↓ 35-↑ 18%) <sup>b</sup>	↓ 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%) <sup>b</sup>
Saquinavir SGC <sup>c</sup>	1200 mg q8h x 10 days	600 mg qd x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%) <sup>b</sup>
Tenofovir <sup>d</sup>	300 mg qd	600 mg qd x 14 days	30	↔	↔	↔
Boceprevir	800 mg tid	600 mg qd	NA	↑ 11%	↑ 20%	NA



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

**Table 6: Effect of Coadministered Drug on Efavirenz Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

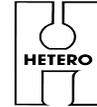
Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
	x 6 days	x 16 days		(2-20%)	(15-26%)	
Telaprevir	750 mg	600 mg qd	21	↓ 16%	↓ 7%	↓ 2%
	q8h x 10 days	x 20 days		(7-24%)	(2-13%)	(↓ 6-↑ 2%)
Telaprevir, coadministered with tenofovir disoproxil fumarate (TDF)	1125 mg	600 mg	15	↓ 24%	↓ 18%	↓ 10%
	q8h x 7 days	efavirenz /300 mg TDF qd x 7 days		(15-32%)	(10-26%)	(↓ 19-↑ 1%)
	1500 mg	600 mg	16	↓ 20%	↓ 15%	↓ 11%
	q12h x 7 days	efavirenz /300 mg TDF qd x 7 days		(14-26%)	(9-21%)	(4-18%)
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	600 mg qd	12	↓ 20%	↓ 26%	↓ 32%



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

**Table 6: Effect of Coadministered Drug on Efavirenz Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
	7 days	x 7 days		(11-28%)	(15-36%)	(15-46%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↑ 38% <sup>c</sup>	↑ 44% <sup>c</sup>	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 14% <sup>f</sup> (7-21%)	↔ <sup>f</sup>	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↔ <sup>f</sup>	↑ 17% <sup>f</sup> (6-29%)	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	↔	↔	↔
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	30 mL single dose	400 mg single dose	17	↔	↔	NA

**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg****Table 6: Effect of Coadministered Drug on Efavirenz Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
simethicone						
40 mg						
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days	600 mg qd x 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 x 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%)	↔	↔

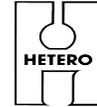
↑ Indicates increase   ↓ Indicates decrease   ↔ Indicates no change or a mean increase or decrease of <10%.

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

b 95% CI.

c Soft Gelatin Capsule.

d Tenofovir disoproxil fumarate.



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

**Table 6: Effect of Coadministered Drug on Efavirenz Plasma C<sub>max</sub>, AUC, and C<sub>min</sub>**

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)

e 90% CI not available.

f Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).

NA = not available.

*Lamivudine:*

There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects

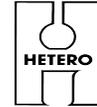
*In vitro* data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction 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-1/HCV co-infected patients [see Warnings and Precautions (5.4)].

Lamivudine and TMP/SMX were coadministered 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<sub>∞</sub>, 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 [see Drug Interactions (7.2)].

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-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:*

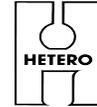
**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg**

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 disoproxil fumarate with other medicinal products is low.

Tenofovir Disoproxil Fumarate has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 7 and 8 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug. No clinically significant drug interactions have been observed between tenofovir and efavirenz, methadone, nelfinavir, oral contraceptives, or ribavirin.

**Table 7 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir<sup>a</sup> in the Presence of the Coadministered Drug**

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters <sup>b</sup> (90% CI)		
			C <sub>max</sub>	AUC	C <sub>min</sub>
Abacavir	300 once	8	↔	↔	NC
Atazanavir <sup>c</sup>	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine <sup>d</sup>	250 or 400 once daily × 7 days	14	↔	↔	↔
Emtricitabine	200 once daily × 7 days	17	↔	↔	↔
Entecavir	1 mg once daily x 10 days	28	↔	↔	↔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↔	↔	↔
Lopinavir/Ritonavir	400/100 twice daily × 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 65)



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

					66)
Saquinavir/Ritonavir	1000/100 twice daily × 14 days	35	↔	↔	↑ 23 (↑ 16 to ↑ 30)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔

<sup>a</sup> Subjects received tenofovir disoproxil fumarate 300 mg once daily.

<sup>b</sup> Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated

<sup>c</sup> Reyataz (atazanavir) Prescribing Information

<sup>d</sup> Subjects received didanosine buffered tablets.

Following multiple dosing to HIV-1 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 studies, indicating lack of clinically significant drug interactions between these agents and tenofovir disoproxil fumarate.

**Table 8 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 <sup>a</sup> (90% CI)		
			C <sub>max</sub>	AUC	C <sub>min</sub>
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	↔	NA
Atazanavir <sup>b</sup>	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters <sup>a</sup> (90% CI)		
			C <sub>max</sub>	AUC	C <sub>min</sub>
Atazanavir <sup>b</sup>	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25 <sup>c</sup> (↓ 42 to ↓ 3)	↓ 23 <sup>c</sup> (↓ 46 to ↑ 10)
Didanosine <sup>d</sup>	250 once, simultaneously with	33	↓ 20 <sup>f</sup> (↓ 32 to ↓ 7)	↔ <sup>f</sup>	NA

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

	tenofovir and a light meal <sup>e</sup>				
Emtricitabine	200 once daily × 7 days	17	↔	↔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily x 10 days	28	↔	↑ 13 (↑ 11 to ↑ 15)	↔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	↔	↔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔
Ritonavir			↔	↔	↔
Saquinavir			↑ 22 (↑ 6 to ↑ 41)	↑ 29 <sup>g</sup> (↑ 12 to ↑ 48)	↑ 47 <sup>g</sup> (↑ 23 to ↑ 76)
Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↔	↔	↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↔	↔	↔

<sup>a</sup> Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable

<sup>b</sup> Reyataz (atazanavir) Prescribing Information

<sup>c</sup> In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C<sub>min</sub> values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

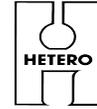
<sup>d</sup> Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules.

<sup>e</sup> 373 kcal, 8.2 g fat

<sup>f</sup> Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.

<sup>g</sup> Increases in AUC and C<sub>min</sub> are not expected to be clinically relevant; hence no dose

adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered



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

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Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution [See *Drug Interactions (7.3)*]. When administered with multiple doses of tenofovir disoproxil fumarate, the  $C_{max}$  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 enteric-coated capsules alone under fasted conditions.

### **5.3 Preclinical safety data**

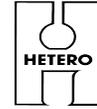
#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

**Lamivudine:** Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma



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levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

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

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

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

### **Animal Toxicology and/or Pharmacology**

*Efavirenz:* Nonsustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose [see *Warnings and Precautions (5.12)*].

*Lamivudine:* Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

*Tenofovir Disoproxil Fumarate:* Tenofovir and Tenofovir Disoproxil Fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon

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dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

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

**6. PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

**Tablets contents:** Pregelatinized Starch, Lactose Hydroxypropyl Cellulose (Klucel LF), microcrystalline Cellulose (Vivapur 102), Croscarmellose Sodium, Purified water, Magnesium Stearate (LIGAMED MF-2-V), Opadry II Yellow 85F520012.

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

24 months

**6.4 Special precautions for storage**

Store below 30°C and protect from moisture.

**6.5 Nature and contents of container**

HDPE container pack of 30's count

**6.6 Special precautions for disposal and other handling**

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



**Hetero**

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**7. Marketing Authorisation Holder and Manufacturing Site Addresses**

**Marketing authorization Holder:**

**Name:** Hetero Labs Limited

**Business Address:** 7-2-A2, Hetero Corporate, Industrial Estates, Sanath Nagar,  
Hyderabad-500 018, Telangana. India

Telephone : +91-40-23704923/24/25

Telefax : +91-40-23704035/23813359

E-Mail : [contact@heterodrugs.com](mailto:contact@heterodrugs.com)

**Manufacturing site:**

(Company) Name : Hetero Labs Limited (Unit-III)

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Pin Code - 500 055,  
Telangana, India

Telephone : +91 40-23096171/172/173/174

Telefax : + 91 40-23095105

E-Mail : [contact@heterodrugs.com](mailto:contact@heterodrugs.com)

**8. Marketing authorization number**

**9. Date of first registration/renewal of the registration**

**10. Date of revision of the text**