For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

FULL PRESCRIBING INFORMATION

Trustiva

Tenofovir Disoproxil Fumarate, Efavirenz & Emtricitabine Tablets IP

300 mg/600 mg /200 mg

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST-TREATMENT EXACERBATION OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of TRUSTIVA, in combination with other antiretrovirals [See Warnings and Precautions (5.1)].

TRUSTIVA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of TRUSTIVA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued emtricitabine or tenofovir DF , which are components of TRUSTIVA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue TRUSTIVA. If appropriate, initiation of anti-hepatitis B therapy may be warranted [See Warnings and Precautions (5.2)].

Composition:

Each film-coated tablet contains:
Tenofovir disoproxil fumarate IP.. 300 mg
(eq. to Tenofovir disoproxil 245 mg)
Efavirenz IP................................. 600 mg
Emtricitabine IP........................... 200 mg
Excipient... q.s

Colours: Ferric Oxide USP-NF Red,
Black oxide of Iron & Titanium Dioxide IP

1. INDICATIONS AND USAGE

Trustiva (efavirenz/emtricitabine/tenofovir disoproxil fumarate) is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

2. DOSAGE AND ADMINISTRATION

Adults and pediatric patients 12 years of age and older with body weight at least 40 kg (at least 88 lbs): The dose of Trustiva is one tablet once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.

Renal Impairment: Because Trustiva is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (estimated creatinine clearance below 50 mL/min).

Rifampin Coadministration: When Trustiva is administered with rifampin to patients weighing 50 kg or more, an additional 200 mg/day of efavirenz is recommended *[See Drug Interactions (7.3), Table 4, and Clinical Pharmacology (11.2), Table 5].*

3 DOSAGE FORMS AND STRENGTHS

Trustiva is available as tablets. Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (tenofovir DF, which is equivalent to 245 mg of tenofovir disoproxil). **The tablets are puff pinkish,** capsule-shaped, film-coated, debossed with "128" on one side and "H" on the other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Trustiva is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz, a component of Trustiva.

4.2 Contraindicated Drugs

For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated with Trustiva are listed in Table 1.

Table 1: Drugs That Are Contraindicated or Not Recommended for Use With Trustiva

Drug Class: Drug Name	Clinical Comment
Antifungal: voriconazole	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. Because Trustiva is a fixed-dose combination product, the dose of efavirenz cannot be altered. [See Clinical Pharmacology (12.3) Tables 5 and 6]
Ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	Potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Benzodiazepines: midazolam, triazolam	Potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort *(Hypericum perforatum)*	May lead to loss of virologic response and possible resistance to efavirenz or to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including tenofovir DF, a component of Trustiva, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Trustiva 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).

5.2 Patients Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic HBV before initiating antiretroviral therapy. Trustiva is not approved for the treatment of chronic HBV infection, and the safety and efficacy of Trustiva have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of Trustiva. In some patients infected with HBV and treated with emtricitabine, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are coinfected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with Trustiva. If appropriate, initiation of anti-hepatitis B therapy may be warranted. Trustiva should not be administered with adefovir dipivoxil *[See Drug Interactions (7.2)].*

5.3 Drug Interactions

Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A. Likewise, efavirenz may alter plasma concentrations of drugs metabolized by CYP3A or CYP2B6 *[See Contraindications (4.2), Drug Interactions (7.1)].*

5.4 Coadministration with Related Products

Related drugs not for coadministration with Trustiva include emtricitabine/rilpivirine/tenofovir DF, emtricitabine, elvitegravir/cobicistat/emtricitabine/tenofovir DF, emtricitabine/tenofovir DF, and tenofovir DF, which contain the same active components as Trustiva.

Efavirenz should not be coadministered with Trustiva unless needed for dose-adjustment (e.g., with rifampin) *[See Dosage and Administration (2), Drug Interactions (7.1)].* Due to similarities between emtricitabine and lamivudine, Trustiva should not be coadministered with drugs containing lamivudine, including lamivudine/zidovudine, lamivudine, or lamivudine-HBV, abacavir sulfate/lamivudine, or abacavir sulfate/lamivudine/zidovudine.

5.5 Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1008 subjects treated with regimens containing efavirenz for a mean of 2.1 years and 635 subjects treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among subjects 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 AI266006 (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 trial 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 trial for both efavirenz-treated and control-treated subjects. One percent of efavirenz-treated subjects 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 *[See Adverse Reactions (6)].*

5.6 Nervous System Symptoms

Fifty-three percent (531/1008) of subjects receiving efavirenz in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of subjects receiving control regimens. These symptoms included dizziness (28.1% of the 1008 subjects), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). Other reported symptoms were euphoria, confusion, agitation, amnesia, stupor, abnormal thinking, and depersonalization. The majority of these symptoms were mild-to-moderate (50.7%); symptoms were severe in 2.0% of subjects. Overall, 2.1% of subjects discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2–4 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 subjects treated with regimens containing efavirenz and from 3% to 5% in subjects 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 (5.5)].* Dosing at bedtime may improve the tolerability of these nervous system symptoms *[See Dosage and Administration (2)].*

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

Patients receiving Trustiva should be alerted to the potential for additive central nervous system effects when Trustiva 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.

5.7 New Onset or Worsening Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney; however, efavirenz is not. Since Trustiva is a combination product and the dose of the individual components cannot be altered, patients with estimated creatinine clearance below 50 mL/min should not receive Trustiva.

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 DF *[See Adverse Reactions (6.3)].*

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

Trustiva should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) *[See Drug Interactions (7.2)].* Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

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

5.8 Reproductive Risk Potential

Pregnancy Category D: Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving Trustiva. Barrier contraception must always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of Trustiva is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of Trustiva. 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 trials of Trustiva in pregnant women. Trustiva 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 *[See Use in Specific Populations (8.1)].*

5.9 Rash

In controlled clinical trials, 26% (266/1008) of subjects treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (111/635) of subjects treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of subjects treated with efavirenz. The incidence of Grade 4 rash (e.g., erythema multiforme, Stevens-Johnson syndrome) in subjects treated with efavirenz in all trials 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 subjects continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 1.7% (17/1008). Trustiva can be reinitiated in patients interrupting therapy because of rash. Trustiva should be discontinued in patients developing severe rash associated with b lis te ring , 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 (e.g., Stevens-Johnson syndrome), alternative therapy should be considered *[See also Contraindications (4.1)].*

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

Rash was reported in 26 of 57 pediatric subjects (46%) treated with efavirenz *[See Adverse Reactions (6.1)].* One pediatric subject experienced Grade 3 rash (confluent rash with fever), and two subjects had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric subjects was 8 days. Prophylaxis with appropriate antihistamines before initiating therapy with ATRI PLA in pediatric patients should be considered.

5.10 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 also Warnings and Precautions (5.2)].* 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 (6.3)].* 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 Trustiva needs to be weighed against the unknown risks of significant liver toxicity *[See Adverse Reactions (6.2)].*

5.11 Bone Effects of Tenofovir DF

Bone Mineral Density:

In clinical trials in HIV-1 infected adults, tenofovir DF was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir DF.

Clinical trials evaluating tenofovir DF in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir DF treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected. For more information, consult the tenofovir DF prescribing information.

The effects of tenofovir DF-associated changes in BM D and biochemical markers on lo n g-term bo ne health and future fractur e risk a re un known. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vi tamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects:

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir DF *[See Adverse Reactions (6.3)].* Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF *[See Warnings and Precautions (5.7)].*

5.12 Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Caution must be taken in any patient with a history of seizures.

Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels *[See Drug Interactions (7.3)].*

5.13 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of Trustiva. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.14 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy.

The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

6 ADVERSE REACTIONS

Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate: The following adverse reactions are discussed in other sections of the labeling:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions (5.1)].*
- Severe Acute Exacerbations of Hepatitis B *[See Boxed Warning, Warnings and Precautions (5.2)].*
- Psychiatric Symptoms *[See Warnings and Precautions (5.5)].*
- Nervous System Symptoms *[See Warnings and Precautions (5.6)].*
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.7)].*
- Rash *[See Warnings and Precautions (5.9)].*
- Hepatotoxicity *[See Warnings and Precautions (5.10)].*
- Bone Effects of Tenofovir DF *[See Warnings and Precautions (5.11)].*
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.13)].*
- Drug Interactions *[See Contraindications (4.2), Warnings and Precautions (5.3) and Drug Interactions (7)].*

For additional safety information about efavirenz, emtricitabine, or tenofovir DF in combination with other antiretroviral agents, consult the prescribing information for these products.

6.1 Adverse Reactions from Clinical Trials Experience

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

Clinical Trials in Adult Subjects

Study 934

Study 934 was an open-label active-controlled trial in which 511 antiretroviral-naive subjects received either emtricitabine + tenofovir DF administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254).

The most common adverse reactions (incidence greater than or equal to 10%, any severity) occurring in Study 934 include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. Adverse reactions observed in Study 934 were generally consistent with those seen in previous trials of the individual
components (Table 2).

Table 2: Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥ 5% in Either Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV[b] N=257	AZT/3TC + EFV N=254
Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorder and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis	8%	4%
Upper Respiratory tract infections	8%	5%
Nasopharyngitis	5%	3%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Anxiety	5%	4%
Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders		
Rash Event[c]	7%	9%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug. b. From Weeks 96 to 144 of the trial, subjects received emtricitabine/tenofovir DF administered in combination with efavirenz in place of emtricitabine + tenofovir DF with efavirenz. c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculopapular, rash pruritic, and rash vesicular.

Study 073

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

Efavirenz, Emtricitabine, or Tenofovir Disoproxil Fumarate

In addition to the adverse reactions in Study 934 and Study 073, the following adverse reactions were observed in clinical trials of efavirenz, emtricitabine, or tenofovir DF in combination with other antiretroviral agents.

Efavirenz: The most significant adverse reactions observed in subjects treated with efavirenz are nervous system symptoms *[See Warnings and Precautions (5.6)]*, psychiatric symptoms *[See Warnings and Precautions (5.5)]*, and rash *[See Warnings and Precautions (5.9)].*

Selected adverse reactions of moderate-to-severe intensity observed in greater than or equal to 2% of efavirenz-treated subjects in two controlled clinical trials included pain, impaired concentration, abnormal dreams, somnolence, anorexia, dyspepsia, abdominal pain, nervousness, and pruritus.

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

Emtricitabine and Tenofovir Disoproxil Fumarate: Adverse reactions that occurred in at least 5% of treatment-experienced or treatment-naive subjects receiving emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials include arthralgia, increased cough, dyspepsia, fever, myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, rhinitis and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction).

Skin discoloration has been reported with higher frequency among emtricitabine-treated subjects; it was manifested by hyperpigmentation on the palms and/or soles and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Clinical Trials in Pediatric Subjects

Efavirenz: In a pediatric clinical trial in 57 NRTI-experienced subjects aged 3 to 16 years, the type and frequency of adverse experiences was generally similar to that of adult subjects with the exception of a higher incidence of rash, which was reported in 46% (26/57) of pediatric subjects compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric subjects compared to 0.9% of adults *[See Warnings and Precautions (5.9)].* For additional information, please consult the efavirenz prescribing information.

Emtricitabine: In addition to the adverse reactions reported in adults, anemia and hyperpigmentation were observed in 7% and 32%, respectively, of pediatric subjects (3 months to less than 18 years of age) who received treatment with emtricitabine in the larger of two open-label, uncontrolled pediatric trials (N=116). For additional information, please consult the emtricitabine prescribing information.

Tenofovir Disoproxil Fumarate: In a pediatric clinical trial conducted in subjects 12 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with tenofovir DF were consistent with those observed in clinical trials of tenofovir DF in adults *[See Warnings and Precautions (5.11)].*

6.2 Laboratory Abnormalities

Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate: Laboratory abnormalities observed in Study 934 were generally consistent with those seen in previous trials (Table 3)

Table 3: Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Either Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV[a] N=257	AZT/3TC + EFV N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm³)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

Hepatic Events: In Study 934, 19 subjects treated with efavirenz, emtricitabine, and tenofovir DF and 20 subjects treated with efavirenz and fixed-dose zidovudine/lamivudine were hepatitis B surface antigen or hepatitis C antibody positive. Among these coinfected subjects, one subject (1/19) in the efavirenz, emtricitabine and tenofovir DF arm had elevations in transaminases to greater than five times ULN through 144 weeks. In the fixed-dose zidovudine/lamivudine arm, two subjects (2/20) had elevations in transaminases to greater than five times ULN through 144 weeks. No HBV and/or HCV coinfected subject discontinued from the trial due to hepatobiliary disorders *[See Warnings and Precautions (5.10)].*

6.3 Postmarketing Experience

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

Efavirenz:

Cardiac Disorders: Palpitations

Ear and Labyrinth Disorders: Tinnitus, vertigo

Endocrine Disorders: Gynecomastia

Eye Disorders: Abnormal vision

Gastrointestinal Disorders: Constipation, malabsorption

General Disorders and Administration Site Conditions: Asthenia

Hepatobiliary Disorders: 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.

Immune System Disorders: Allergic reactions

Metabolism and Nutrition Disorders: Redistribution/accumulation of body fat *[See Warnings and Precautions (5.14)]*, hypercholesterolemia, hypertriglyceridemia Musculoskeletal and Connective Tissue Disorders: Arthralgia, myalgia, myopathy

Nervous System Disorders: Abnormal coordination, ataxia, cerebellar coordination and balance disturbances, convulsions, hypoesthesia, paresthesia, neuropathy, tremor

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

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Flushing, erythema multiforme, photoallergic dermatitis, Stevens-Johnson syndrome

Emtricitabine: No postmarketing adverse reactions have been identified for inclusion in this section.

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

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

Skin and Subcutaneous Tissue Disorders: Rash

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy Renal and Urinary Disorders: Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions: Asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

7 DRUG INTERACTIONS

This section describes clinically relevant drug interactions with Trustiva. Drug interaction trials are described elsewhere in the labeling *[See Clinical Pharmacology (11.2)].*

7.1 Efavirenz

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 (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz, resulting in lowered plasma concentrations *[See Dosage and Administration (2)].*

7.2 Emtricitabine and Tenofovir Disoproxil Fumarate

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of Trustiva with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine,tenofovir, and/or other renally eliminated drugs. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[See Warnings and Precautions (5.7)].*

Coadministration of tenofovir DF 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 [for didanosine dosing adjustment recommendations, see *Table 4*]. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily.

Darunavir with ritonavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. Tenofovir DF is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir DF is co-administered with an inhibitor of these transporters, an increase in absorption may be observed. Patientsreceiving darunavir with ritonavir and Trustiva, or lopinavir/ritonavir with Trustiva, should be monitored for tenofovir-associated adverse reactions. Trustiva should be discontinued in patients who develop tenofovir-associated adverse reactions *[See Table 4].*

Coadministration of atazanavir with Trustiva is not recommended since coadministration of atazanavir with either efavirenz or tenofovir DF has been shown to decrease plasma concentrations of atazanavir. Also, atazanavir has been shown to increase tenofovir concentrations. There are insufficient data to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with Trustiva *[See Table 4].*

7.3 Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate

Other important drug interaction information for Trustiva is summarized in Table 1 and Table 4. The drug interactions described are based on trials conducted with efavirenz, emtricitabine or tenofovir DF as individual agents or are potential drug interactions; no drug interaction trials have been conducted using Trustiva [for pharmacokinetics data see *Clinical Pharmacology (11.2)*, Tables 5-8]. The tables include potentially significant interactions, but are not all inclusive.

Table 4: Established and Other Potentially Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
HIV antiviral agents		
Protease inhibitor: atazanavir	↓ atazanavir ↑ tenofovir	Coadministration of atazanavir with Trustiva is not recommended Coadministration of atazanavir with either efavirenz or tenofovir DF decreases plasma concentrations of atazanavir. The combined effect of efavirenz plus tenofovir DF on atazanavir plasma concentrations is not known. Also, atazanavir has been shown to increase tenofovir concentrations. There are insufficient data to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with Trustiva.
Protease inhibitor: fosamprenavir calcium	↓ amprenavir	Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and Trustiva 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 Trustiva is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when Trustiva is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: indinavir	↓ indinavir	The optimal dose of indinavir; when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Protease inhibitor: lopinavir/ritonavir	↓ lopinavir ↑ tenofovir	Do not use once daily administration of lopinavir/ritonavir. Dose adjustment of lopinavir/ritonavir is recommended when coadministered with efavirenz. Refer to the full prescribing information for lopinavir/ritonavir for guidance on coadministration with efavirenz- or tenofovir- containing regimens, such as Trustiva. Patients should be monitored for tenofovir- associated adverse reactions.
Protease inhibitor: ritonavir	↑ ritonavir ↑ efavirenz	When ritonavir 500 mg every 12 hours was coadministered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when Trustiva is used in combination with ritonavir.
Protease inhibitor: saquinavir	↓ saquinavir	Appropriate doses of the combination of efavirenz and saquinavir/ritonavir with respect to safety and efficacy have not been established
CCR5 co-receptor antagonist:	↓ maraviroc	Efavirenz decreases plasma maraviroc concentrations of maraviroc. Refer to the full prescribing information for maraviroc for guidance on coadministration with Trustiva
NRTI: didanosine	↑ didanosine	Coadministration of Trustiva and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions including pancreatitis, lactic acidosis, and neuropathy. A dose reduction of didanosine is recommended when coadministered with tenofovir DF. For additional information on coadministration with tenofovir DF- containing products, please refer to the didanosine prescribing information.
NNRTI: Other NNRTIs with other NNRTIs.	↓ or ↑ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. Trustiva contains efavirenz and should not be coadministered
Integrase strand transfer inhibitor: raltegravir	↓ raltegravir	Efavirenz reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.
Hepatitis C antiviral agents		
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.
Protease inhibitor: telaprevir	↓ telaprevir ↓ efavirenz	Concomitant administration of telaprevir and efavirenz resulted in reduced steady-state exposures to telaprevir and efavirenz.
Anticoagulant: warfarin	↑ or ↓ warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Other agents		
Anticonvulsants: carbamazepine	↓ carbamazepine ↓ efavirenz	There are insufficient data to make a dose recommendations for Trustiva. Alternative anticonvulsant treatment should be used.
phenytoin phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants: bupropion	↓ bupropion	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.
sertraline	↓ sertraline	Increases in sertraline dose should be guided by clinical response.
Antifungals: itraconazole	↓ itraconazole ↓ hydroxy-itraconazole	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
ketoconazole	↓ ketoconazole	Drug interaction trials with Trustiva and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
posaconazole	↓ posaconazole	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: clarithromycin	↓ clarithromycin ↑ 14-OH metabolite	Clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of Trustiva is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics, such as erthromycin, have not been studied in combination with Trustiva.
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 Trustiva is coadministered with rifampin to patients weighing 50 kg or more, an additional 200 mg/day of efavirenz 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 Trustiva is necessary when administered with diltiazem.
Others (e.g., felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the full prescribing information for the calcium channel blockers)
HMG-CoA reductase inhibitors: atorvastatin pravastatin simvastatin	↓ atorvastatin ↓ pravastatin ↓ simvastatin	Plasma concentrations of atorvastatin, pravastatin and simvastatin decreased with efavirenz. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Oral: ethinyl estradiol/ norgestimate	↓ active metabolites of norgestimate	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.
Implant: etonogestrel	↓ etonogestrel	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	↓ immuno-suppressant	Decreased exposure of the immunosuppressant may be expected due to CYP3A induction by efavirenz. These immunosuppressant 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 Trustiva.
Narcotic analgesic: methadone	↓ methadone	Coadministration of efavirenz in HIV-1 infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

a. This table is not all inclusive.

7.4 Efavirenz Assay Interference

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 Micro genics 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. For more information, please consult the efavirenz prescribing information.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[See Warnings and Precautions (5.8)]*

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 reported defects with first-trimester exposure was a neural tube defect. A single case of an ophthalmia 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 meningo myelocele. 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, microophthalmia in a second, and cleft palate in the third.

There was no NOAEL (no observable adverse effect level) established for this study because only one dosage was evaluated. In rats, efavirenz was administered either during organogenesis (gestation Days 7 to 18) or from gestation Day 7 through lactation Day 21 at 50, 100, or 200 mg/kg/day. Administration of 200 mg/kg/day in rats was associated with an 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.

8.2 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. Studies in rats have demonstrated that efavirenz is secreted in milk. Studies in humans have shown that both tenofovir and emtricitabine are excreted in human milk. Because the risks of low level exposure to emtricitabine and tenofovir to infants are unknown, and because of the potential for HIV-1 transmission, **mothers should be instructed not to breastfeed if they are receiving Trustiva.**

Emtricitabine

Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Tenofovir Disoproxil Fumarate

Samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk. Tenofovir-associated risks, including the risk of viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown.

8.3 Pediatric Use

Trustiva should only be administered to pediatric patients 12 years of age and older with a body weight greater than or equal to 40 kg (greater than or equal to 88 lbs).

Because Trustiva is a fixed-dose combination tablet, the dose adjustments recommended for pediatric patients younger than 12 years of age for each individual component cannot be made with Trustiva *[See Warnings and Precautions (5.9, 5.11), Adverse Reactions (6.1) and Clinical Pharmacology (12.3)].*

8.4 Geriatric Use

Clinical trials of efavirenz, emtricitabine, or tenofovir DF 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 elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.5 Hepatic Impairment

Trustiva is not recommended for patients with moderate or severe hepatic impairment because there are insufficient data to determine an appropriate dose. Patients with mild hepatic impairment may be treated with Trustiva at the approved 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 Trustiva to these patients *[See Warnings and Precautions (5.10) and Clinical Pharmacology (12.3)].*

8.6 Renal Impairment

Because Trustiva is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (estimated creatinine clearance below 50 mL/min) *[See Warnings and Precautions (5.7)].*

10 OVERDOSAGE

If overdose occurs, the patient should be monitored for evidence of toxicity, including monitoring of vital signs and observation of the patient's clinical status; standard supportive treatment should then be applied as necessary. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. Hemodialysis can remove both emtricitabine and tenofovir DF (refer to detailed information below), but is unlikely to significantly remove efavirenz from the blood.

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

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology trial single doses of emtricitabine 1200 mg were administered to 11 subjects. No severe adverse reactions

were reported.

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

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of tenofovir DF 300 mg is available. In one trial, 600 mg tenofovir DF was administered to 8 subjects orally for 28 days, and 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 DF, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

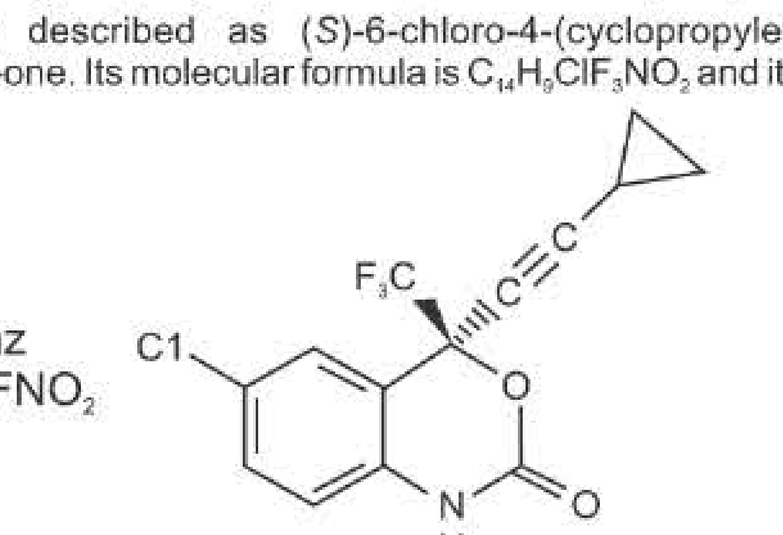
11 DESCRIPTION

Trustiva is a fixed-dose combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate (tenofovir DF). Efavirenz, a non-nucleoside reverse transcriptase inhibitor. Emtricitabine, a synthetic nucleoside analog of cytidine. Tenofovir DF, which is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.

Trustiva tablets are for oral administration. Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients. The tablets include the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablets are film-coated with a coating material containing black iron oxide, polyethylene glycol, polyvinyl alcohol, red iron oxide, talc, and titanium dioxide.

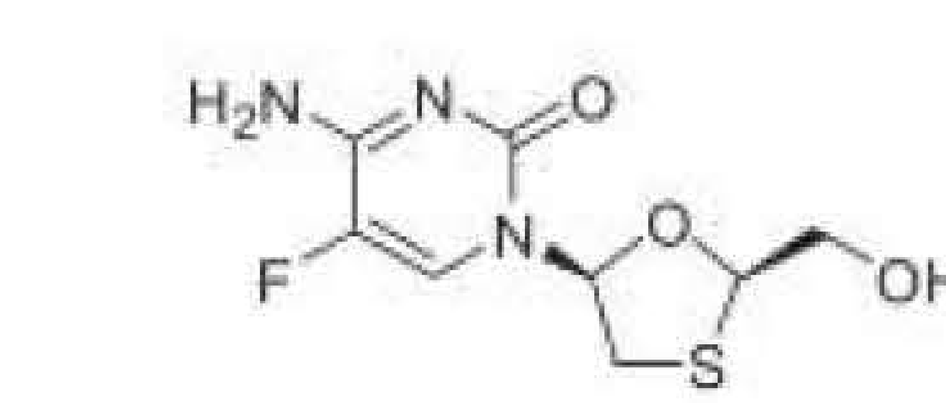
Efavirenz: Efavirenz is chemically described as (*S*)-6-chloro-4-(cyclopropylethynyl) -1,4-dihydro-4-(trifluoromethyl) -2*H*-3,1-benzoxazin-2-one. Its molecular formula is $C_{14}H_9ClF_3NO_2$ and its structural formula is:

Efavirenz
$C_{14}H_9ClFNO_2$



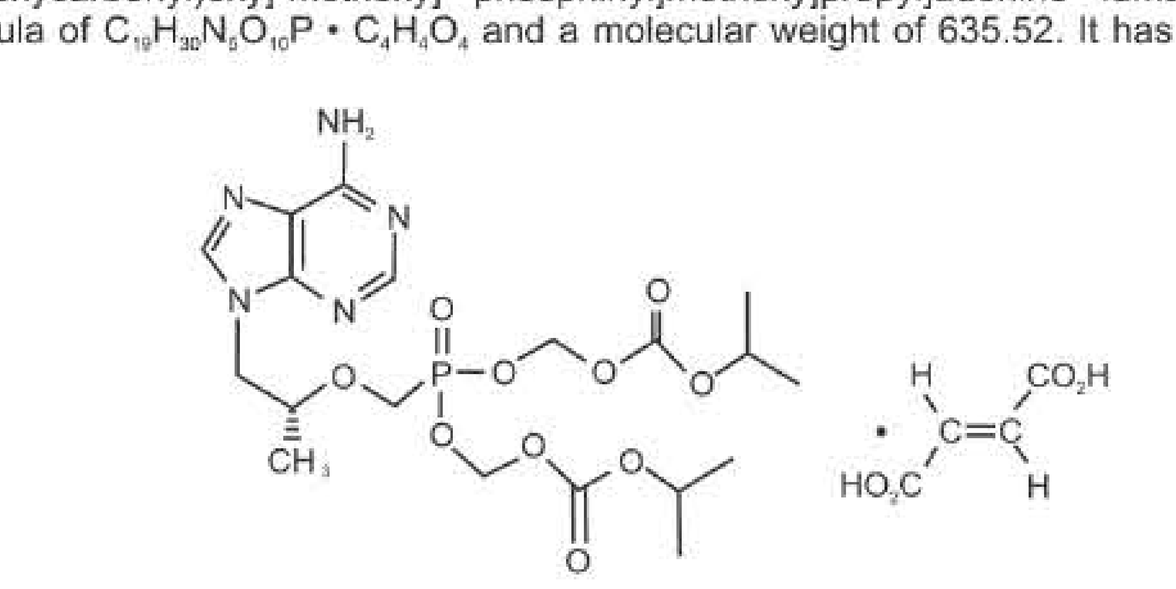
Efavirenz is a white to slightly pink crystalline powder with a molecular mass of 315.68. It is practically insoluble in water (less than 10 µg/mL).

Emtricitabine: The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2- (hydroxymethyl)-1,3-oxathiolan- 5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position. It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25°C.

Tenofovir Disoproxil Fumarate: Tenofovir DF is a fumaric acid salt of the *bis*isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2[[bis[[(isopropoxycarbonyl)oxy]-methoxy] phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C.

12 CLINICAL PHARMACOLOGY

For additional information on Mechanism of Action, Antiviral Activity, Resistance and Cross Resistance, please consult the efavirenz, emtricitabine and tenofovir DF prescribing information.

12.1 Mechanism of Action

Trustiva is a fixed-dose combination of antiviral drugs efavirenz, emtricitabine and tenofovir disoproxil fumarate *[See Clinical Pharmacology (12.4)].*

12.3 Pharmacokinetics

Trustiva: One Trustiva tablet is bioequivalent to one efavirenz tablet (600 mg) plus one emtricitabine capsule (200 mg) plus one tenofovir DF tablet (300 mg) following single-dose administration to fasting healthy subjects (N=45).

Efavirenz: In HIV-1 infected subjects time-to-peak plasma concentrations were approximately 3–5 hours and steady-state plasma concentrations were reached in 6–10 days. In 35 HIV-1 infected subjects receiving efavirenz 600 mg once daily, steady-state Cmax was 12.9 ± 3.7 μM (mean ± SD), Cmin was 5.6 ± 3.2 μM, and AUC was 184 ± 73 μM•hr. Efavirenz is highly bound (approximately 99.5–99.75%) to human plasma proteins, predominantly albumin. Following administration of ^{14}C-labeled efavirenz, 14–34% of the dose was recovered in the urine (mostly as metabolites) and 16–61% 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 52–76 hours after single doses and 40–55 hours after multiple doses.

Emtricitabine: Following oral administration, emtricitabine is rapidly absorbed, with peak plasma concentrations occurring at 1–2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected subjects, the steady state plasma emtricitabine Cmax was 1.8 ± 0.7 μg/mL (mean ± SD) and the AUC over a 24-hour dosing interval was 10.0 ± 3.1 μg•hr/mL. The mean steady-state plasma trough concentration at 24 hours post-dose was 0.09 μg/mL. The mean absolute bioavailability of emtricitabine was 93%. Less than 4% of emtricitabine binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.02–200 μg/mL. Following administration of radio labelled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 213 ± 89 mL/min (mean ± SD). Following a single oral dose, the plasma emtricitabine half-life is approximately 10 hours.

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 (Cmax) were achieved in 1.0 ± 0.4 hrs (mean ± SD) and Cmax and AUC values were 296 ± 90 ng/mL and 2287 ± 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 0.01–25 μg/mL. Approximately 70–80% 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 ± 33 mL/min (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effects of Food on Oral Absorption

Trustiva has not been evaluated in the presence of food. Administration of efavirenz tablets with a high fat meal increased the mean AUC and Cmax of efavirenz by 28% and 79%, respectively, compared to administration in the fasted state. Compared to fasted administration, dosing of tenofovir DF and emtricitabine in combination with

either a high fat meal or a light meal increased the mean AUC and Cmax of tenofovir by 35% and 15%, respectively, without affecting emtricitabine exposures *[See Dosage and Administration (2) and Patient Counseling Information (17.7)].*

Special Populations

Race

Efavirenz: The pharmacokinetics of efavirenz in HIV-1 infected subjects appear to be similar among the racial groups studied.

Emtricitabine: No pharmacokinetic differences due to race have been identified following the administration of emtricitabine.

Tenofovir Disoproxil Fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir DF.

Gender

Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate: Efavirenz, emtricitabine, and tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric Patients

Trustiva should only be administered to pediatric patients 12 years of age and weighing greater than or equal to 40 kg (greater than or equal to 88 lb).

Efavirenz: In an open-label trial in NRTI-experienced pediatric subjects (mean age 8 years, range 3-16), the pharmacokinetics of efavirenz in pediatric subjects were similar to the pharmacokinetics in adults who received a 600 mg daily dose of efavirenz. In 48 pediatric subjects, receiving the equivalent of a 600 mg dose of efavirenz, mean (± SD) steady-state Cmax was 14.2 ± 5.8 μM, steady-state Cmin was 5.6 ± 4.1 μM, and AUC was 218 ± 104 μM•hr.

Emtricitabine: The pharmacokinetics of emtricitabine at steady state were determined in 27 HIV-1-infected pediatric subjects 13 to 17 years of age receiving a daily dose of 6 mg/kg up to a maximum dose of 240 mg oral solution or a 200 mg capsule; 26 of 27 subjects in this age group received the 200 mg emtricitabine capsule. Mean (± SD) Cmax and AUC were 2.7 ± 0.9 μg/mL and 12.6 ± 5.4 μg•hr/mL, respectively. Exposures achieved in pediatric subjects 12 to less than 18 years of age were similar to those achieved in adults receiving a once daily dose of 200 mg.

Tenofovir Disoproxil Fumarate: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected pediatric subjects (12 to less than 18 years). Mean (± SD) Cmax and AUCtau are 0.38 ± 0.13 μg/mL and 3.39 ± 1.22 μg•hr/mL, respectively. Tenofovir exposure achieved in these pediatric subjects receiving oral daily doses of tenofovir DF 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir DF 300 mg.

Geriatric Patients

Pharmacokinetics of efavirenz, emtricitabine and tenofovir have not been fully evaluated in the elderly (65 years of age and older) *[See Use in Specific Populations (8.4)].*

Patients with Impaired Renal Function

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

Emtricitabine and Tenofovir Disoproxil Fumarate: The pharmacokinetics of emtricitabine and tenofovir DF are altered in subjects with renal impairment. In subjects with creatinine clearance below 50 mL/min, Cmax and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased *[See Warnings and Precautions (5.7)].*

Patients with Hepatic Impairment

Efavirenz: A multiple-dose trial showed no significant effect on efavirenz pharmacokinetics in subjects 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 *[See Warnings and Precautions (5.10) and Use in Specific Populations (8.5)].*

Emtricitabine: The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

Assessment of Drug Interactions

The drug interaction trials described were conducted with efavirenz, emtricitabine, or tenofovir DF as individual agents; no drug interaction trials have been conducted using Trustiva.

Efavirenz: The steady-state pharmacokinetics of efavirenz and tenofovir were unaffected when efavirenz and tenofovir DF were administered together versus each agent dosed alone. Specific drug interaction trials have not been performed with efavirenz and NRTIs other than tenofovir, lamivudine, and zidovudine. Clinically significant interactions would not be expected based on NRTIs elimination pathways.

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 (8.5–17 μM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82–160 μM) only at concentrations well above those achieved clinically. Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A4 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 trials were performed with efavirenz and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. There was no clinically significant interaction observed between efavirenz and zidovudine, lamivudine, azithromycin, fluconazole, lorazepam, cetirizine, or paroxetine. Single doses of famotidine or an aluminum and magnesium antacid with simethicone had no effects on efavirenz exposures. The effects of coadministration of efavirenz on Cmax, AUC, and Cmin are summarized in Table 5 (effect of other drugs on efavirenz) and Table 6 (effect of efavirenz on other drugs). For information regarding clinical recommendations see *Drug Interactions (7).*

Table 5: Drug Interactions: Changes in Pharmacokinetic Parameters for Efavirenz in the Presence of the Coadministered Drug

				Mean % Change of Efavirenz Pharmacokinetic Parameters[a] (90% CI)		
Coadministered Drug	**Dose of Coadministered Drug (mg)**	**Efavirenz Dose (mg)**	**N**	**C_{max}**	**AUC**	**C_{min}**
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[b]	↔	↑16 (↓38 to ↑15)	↑16 (↓42 to ↑20)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↓12 (↓32 to ↑13)c	↓12 (↓35 to ↑18)[c]	↓21 (↓53 to ↑33)
Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	9	↑14 (↑4 to ↑26)	↑21 (↑10 to ↑34)	↑25 (↑7 to ↑46)[c]
Saquinavir SGC[d]	1200 mg q8h x 10 days	600 mg qd x 10 days	13	↓13 (↓ 5 to ↓20)	↓12 (↓ 4 to ↓19)	↓14 (↓ 2 to ↓24)[c]
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↑11 (↑2 to ↑20)	↑20 (↑15 to ↑26)	NA
Telaprevir	750 mg q8h x 10 days	600 mg qd x 20 days	21	↓16 (↓ 7 to ↓24)	↓7 (↓ 2 to ↓13)	↓2 (↓6 to ↑2)
Telaprevir, coadministered with tenofovir disoproxil fumarate (TDF)	1125 mg q8h x 7 days	600 mg efavirenz / 300 mg TDF qd x 7 days	15	↓24 (↓ 15 to ↓32)	↓18 (↓ 10 to ↓26)	↓10 (↓ 19 to ↑1)
	1500 mg q12h x 7 days	600 mg efavirenz / 300 mg TDF qd x 7 days	16	↓20 (↓ 14 to ↓26)	↓15 (↓ 9 to ↓21)	↓11 (↓ 4 to ↓18)
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	12	↑11 (↑3 to ↑19)	↔	↔
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 to ↑1)
Rifampin	600 mg x 7 days	600 mg qd x 7 days	12	↓20 (↓ 11 to ↓28)	↓26 (↓ 15 to ↓36)	↓32 (↓ 15 to ↓46)
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 to ↑8)	↔	↓12 (↓ 25 to ↑3)
Carbamazepine	200 mg qd x 3days, 200 mg bid x 3 days then 400 mg qd x 15 days	600 mg qd x 35 days	14	↓21 (↓ 15 to ↓26)	↓36 (↓ 32 to ↓40)	↓47 (↓ 41 to ↓53)
Diltiazem	240 mg x 14 days	600 mg qd x 28 days	12	↑16 (↑6 to ↑26)	↑11 (↑5 to ↑18)	↑13 (↑1 to ↑26)
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↑11 (↑6 to ↑16)	↔	↔
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↑38[e]	↑44[e]	NA
	300 mg po q12h days 2-7 ↓21)	300 mg qd x 7 days	NA	↓14[f] (↓ 7 to ↑21)	↔[f]	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↔[f]	↑17[f] (↑6 to ↑29)	NA

NA = not available

Increase = ↑; Decrease = ↓; No Effect = ↔. b. Parallel-group design; N for efavirenz + lopinavir/ritonavir, N for efavirenz alone. c. 95% CI. d. Soft Gelatin Capsule. e. 90% CI not available. f. Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).

Table 6: Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Efavirenz

				Mean % Change of Coadministered Drug Pharmacokineti[c] Parameters[a] (90% CI)		
Coadministered Drug	**Dose of Coadministered Drug (mg)**	**Efavirenz Dose (mg)**	**N**	**C_{max}**	**AUC**	**C_{min}**
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓59 (↓ 49 to ↓67)	↓74 (↓ 68 to ↓78)	↓93 (↓ 90 to ↓95)
	400 mg qd d 1-6, then 300 mg qd d 7-20 with ritonovir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7 -20	13	↑14[b] (↓ 17 to ↑58)	↑39[b] (↑2 to ↑88)	↑48[b] (↑24 to ↑76)
	300 mg qd/ ritonavir 100 mg qd d 1-10 (pm), then 400 mg qd/ ritonavir 100 mg gd d 11 -24 (pm) (simultaneous with efavirenz)	600 mg qd with a light snack d 11-24 (pm)	14	↑17 (↑8 to ↑27)	↔	↓42 (↓ 31 to ↓51)
Indinavir	1000 mg q 8h x 10 days	600 mg qd x 10 days	20			
	After morning dose			↔[c]	↓33[c] (↓ 26 to ↓39)	↓39[c] (↓ 24 to ↓51)
	After afternoon dose			↔[c]	↓37[c] (↓ 26 to ↓46)	↓52[c] (↓ 47 to ↓57)
	After evening dose			↓29[c] (↓ 11 to ↓43)	↓46[c] (↓ 37 to ↓54)	↓57[c] (↓ 50 to ↓63)
Lopinavir / Ritonavir	400/100 mg q12h x 9 days	600 mg qd x 9 days	11, 7[d]	↔[e]	↓19[e] (↓ 36 to ↑3)	↓39[e] (↓ 3 to ↓62)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↑21 (↑10 to ↑33)	↑20 (↑8 to ↑34)	↔
Metabolite AG- 1402				↓40 (↓30 to ↓48)	↓37 (↓25 to ↓48)	↓43 (↓21 to ↓59)
Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	11			
	After AM dose			↑24 (↑12 to ↑38)	↑18 (↑6 to ↑33)	↑42 (↑9 to ↑86)[f]
	After PM dose			↔	↔	↑24 (↑3 to ↑50)[f]
Saquinavir SGC[g]	1200 mg q8h x 10 days	600 mg qd x 10 days	12	↓50 (↓ 28 to ↓66)	↓62 (↓ 45 to ↓74)	↓56 (↓ 16 to ↓77)[f]
Maraviroc	100 mg bid	600 mg qd	12	↓51 (↓ 37 to ↓62)	↓45 (↓ 38 to ↓51)	↓45 (↓ 28 to ↓57)
Raltegravir	400 mg single dose	600 mg qd	9	↓36 (↓ 2 to ↓59)	↓36 (↓ 20 to ↓48)	↓21 (↓ 51 to ↑ 28)
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↓8 (↓ 22 to ↑8)	↓19 (↓ 11 to ↓25)	↓44 (↓ 26 to ↓58)
Telaprevir	750 mg q8h x 10 days	600 mg qd x 20 days	21	↓9 (↓ 18 to ↑ 2)	↓26 (↓ 16 to ↓35)	↓47 (↓ 35 to ↓56)
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	11	↓26 (↓ 15 to ↓35)	↓39 ↓ 30 to (↓46)	↓53 (↓ 42 to ↓63)
14 -OH metabolite				↑49 (↑32 to ↑69)	↑34 (↑18 to ↑53)	↑26 (↑9 to ↑45)
Itraconazole	200 mg q12h x 28 days	600 mg qd x 14 days	18	↓37 (↓ 20 to ↓51)	↓39 (↓ 21 to ↓53)	↓44 (↓ 27 to ↓58)
Hydroxy-itraconazole				↓35 (↓12 to ↓52)	↓37 (↓14 to ↓55)	↓43 (↓18 to ↓60)
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg qd x 10 and 20 days	11	↓45 (↓ 34 to ↓53)	↓50 (↓ 40 to ↓57)	NA
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	9	↓32 (↓15 to ↓46)	↓38 (↓28 to ↓47)	↓45 (↓31 to ↓56)
Atorvastatin	100mg qd x 4 days	600 mg qd x 15 days	14	↓14 (↓ 1 to ↓26)	↓43 (↓ 34 to ↓50)	↓69 (↓ 49 to ↓81)
Total active (inculding metabolites)				↓15 (↓2 to ↓26)	↓32 (↓21 to↓41)	↓48 (↓23 to↓64)
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	13	↓32 (↓ 59 to ↑12)	↓44 (↓ 26 to ↓57)	↓19 (↓ 0 to ↓35)
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓72 (↓ 63 to↓79)	↓68 (↓ 62 to↓73)	↓45 (↓ 20 to↓62)
Total active (inculding metabolites)				↓68 (↓ 55 to↓78)	↓60 (↓ 52 to↓68)	Na[h]
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days	600 mg qd x 14 days	12	↓20 (↓ 15 to ↓24)	↓27 (↓ 20 to ↓33)	↓35 (↓ 24 to ↓44)
Epoxide metabolilte				↔	↔	↓13 (↓30 to ↑7)
Diltiazem	240 mg x 21 days	600 mg qd x 14 days	13	↓60 (↓ 50 to ↓68)	↓69 (↓ 55 to ↓79)	↓63 (↓ 44 to ↓75)
Desacetyl diltiazem				↓64 (↓ 57 to ↓69)	↓75 (↓ 59 to ↓84)	↓62 (↓ 44 to ↓75)
N-monodesmethyl diltiazem				↓28 (↓ 7 to ↓44)	↓37 (↓ 17 to ↓52)	↓37 (↓ 17 to ↓52)
Ethinyl estradiol/ Norgestimate	0.035 mg / 0.25 mg x 14 days	600 mg qd x 14 days				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromin			21	↓46 (↓ 39 to ↓52)	↓64 (↓ 62 to ↓67)	↓82 (↓ 79 to ↓85)
Levonorgestrel			6	↓80 (↓ 77 to↓83)	↓83 (↓ 79 to↓87)	↓86 (↓ 80 to↓90)
Methadone	Stable maintenance 35 -100 mg daily	600 mg qd x 14-21 days	11	↓45 (↓ 25 to ↓59)	↓52 (↓ 33 to ↓66)	NA
Bupropion	150 mg single dose (sustained release)	600 mg qd x 14 days	13	↓34 (↓ 21 to ↓47)	↓55 (↓ 48 to ↓62)	NA
Hydroxybupropion				↑50 (↑ 20 to↑80)	↔	NA
Sertraline	50 mg qd x 14 days	600 mg qd x 14-21 days	13	↓29 (↓ 15 to ↓40)	↓39 (↓ 27 to ↓50)	↓46 (↓ 31 to ↓58)
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↓61[i]	↓77[i]	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓36[j] (↓ 21 to ↓49)	↓55[j] (↓ 45 to ↓62)	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↑23[j] (↓1 to ↑53)	↓7[j] (↓23 to ↑13)	NA

NA = not available. a. Increase = ↑; Decrease = ↓; No Effect = ↔. b. Compared with atazanavir 400 mg qd alone. c. Comparator dose of indinavir was 800 mg q8h x 10 days. d. Parallel-group design; N for efavirenz + lopinavir/ritonavir, N for lopinavir/ritonavir alone. e. Values are for lopinavir. The pharmacokinetics of ritonavir 100 mg q12h are unaffected by concurrent efavirenz. f. 95% CI g. Soft Gelatin Capsule. h. Not available because of insufficient data. i. 90% CI not available. j. Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).

Emtricitabine and Tenofovir Disoproxil Fumarate: The steady-state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir DF were administered together versus each agent dosed alone.

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP mediated interactions involving emtricitabine and tenofovir with other medicinal products is low. Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of emtricitabine and tenofovir DF with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug. Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir. No clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, tenofovir DF and zidovudine. Similarly, no clinically significant drug interactions have been observed between tenofovir DF and abacavir, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir or tacrolimus in trials conducted in healthy volunteers. Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy, oral contraceptives, or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous trials, indicating a lack of clinically significant drug interactions between these agents and tenofovir DF.

The effects of coadministered drugs on the Cmax, AUC, and Cmin of tenofovir are shown in Table 7. The effects of coadministration of tenofovir DF on Cmax, AUC, and Cmin of coadministered drugs are shown in Table 8.

Table 7: Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir in the Presence of the Coadministered Drug[a,b]

Coadministered Drug	Dose of Coadministered Drug (mg)	N	Mean % Change of Tenofovir Pharmacokinetic Parametersc (90% CI)		
			C_{max}	**AUC**	**C_{mi}**
Atazanavir[d]	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ritonavir[d]	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/ritonavir[e]	300/100 mg twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Didanosine[f]	250 or 400 once daily x 7 days	14	↔	↔	↔
Lopinavir/ritonavir	400/100 twice daily x 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Tipranavir/ritonavir[g]	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	500/200 twice daily (23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

a. All interaction trials conducted in healthy volunteers. b. Subjects received tenofovir DF 300 mg once daily. c. Increase = ↑; Decrease = ↓; No Effect = ↔. d. Atazanavir Prescribing Information. e. Darunavir Prescribing Information. f. Subjects received didanosine buffered tablets. g. Tirpranavir Prescribing Information.

Table 8: Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate[a,b]

Coadministered Drug	Dose of Coadministered Drug (mg)	N	Mean % Change of Coadministered Drug Pharmacokinetic Parametersc (90% CI)		
			C_{max}	**AUC**	**C_{min}**
Atazanavir[d]	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
	Atazanavir/ritonavir 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25e (↓ 42 to ↓ 3)	↓ 23[e] (↓ 46 to ↑ 10)
Darunavir[f]	Darunavir/ritonavir 300/100 mg once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine[g]	250 once, simultaneously with tenofovir DF and a light meal[h]	33	↓ 20[i] (↓ 32 to ↓ 7)	↔[i]	NA
Lopinavir	Lopinavir/ritonavir 400/100 twice daily x 14 days	24	↔	↔	↔
Ritonavir	Lopinavir/ritonavir 400/100 twice daily x 14 days	24	↔	↔	↔
Tipranavir[j]	Tipranavir/ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

a. All interaction trials conducted in healthy volunteers. b. Subjects received tenofovir DF 300 mg once daily. c. Increase = ↑; Decrease = ↓; No Effect = ↔. d. Atazanavir Prescribing Information. e. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and Cmin values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone. f. Darunavir Prescribing Information. g. Didanosine Prescribing Information. Subjects received didanosine enteric-coated capsules. h. 373 kcal, 8.2 g fat. i. Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions. j. Tirpranavir Prescribing Information.

Coadministration of tenofovir DF with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir DF with didanosine enteric-coated capsules significantly increases the Cmax and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir DF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown [for didanosine dosing adjustment recommendations see *Drug Interactions (7.3)*, Table 4].

12.4 Microbiology

Mechanism of Action

Efavirenz: Efavirenz is a non-nucleoside reverse transcriptase (RT) inhibitor of HIV-1. Efavirenz activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α, β, γ, and δ are not inhibited by efavirenz.

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

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

Antiviral Activity

Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate: In combination studies evaluating the antiviral activity in cell culture of emtricitabine and efavirenz together, efavirenz and tenofovir together, and emtricitabine and tenofovir together, additive to synergistic antiviral effects were observed. *Efavirenz:* The concentration of efavirenz inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90–95% (EC90-95) ranged from 1.7–25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells, and macrophage/monocyte cultures. Efavirenz demonstrated additive antiviral activity against HIV-1 in cell culture when combined with non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine and nevirapine), nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and zidovudine), protease inhibitors (PIs) (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), and the fusion inhibitor enfuvirtide. Efavirenz demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. Efavirenz demonstrated antiviral activity against clade B and most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, and N), but had reduced antiviral activity against group O viruses. Efavirenz is not active against HIV-2.

Emtricitabine: The antiviral activity in cell culture of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC50) values for emtricitabine were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL).

In drug combination studies of emtricitabine with NRTIs (abacavir, lamivudine, stavudine, zalcitabine, and zidovudine), NNRTIs (delavirdine, efavirenz, and nevirapine), and PIs (amprenavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC50 values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC50 values ranged from 0.007–1.5 μM).

Tenofovir Disoproxil Fumarate: The antiviral activity in cell culture of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC50 values for tenofovir were in the range of 0.04–8.5 μM. In drug combination studies of tenofovir with NRTIs (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and zidovudine), NNRTIs (delavirdine, efavirenz, and nevirapine), and PIs (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC50 values ranged from 0.5–2.2 μM) and showed strain specific activity against HIV-2 (EC50 values ranged from 1.6 μM–5.5 μM).

Resistance

Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture and in clinical trials. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT.

In a clinical trial of treatment-naive subjects [*Study 934,* see *Clinical Studies (14)*] resistance analysis was performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuations.

Genotypic resistance to efavirenz, predominantly the K103N substitution, was the most common form of resistance that developed. Resistance to efavirenz occurred in 13/19 analyzed subjects in the emtricitabine + tenofovir DF group and in 21/29 analyzed subjects in the zidovudine/lamivudine fixed-dose combination group. The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 analyzed subject isolates in the emtricitabine + tenofovir DF group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

In a clinical trial of treatment-naive subjects, isolates from 8/47 (17%) analyzed subjects receiving tenofovir DF developed the K65R substitution through 144 weeks of therapy; 7 of these occurred in the first 48 weeks of treatment and one at Week 96. In treatment experienced subjects, 14/304 (5%) of tenofovir DF treated subjects with virologic failure through Week 96 showed greater than 1.4-fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a substitution in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Efavirenz: Clinical isolates with reduced susceptibility in cell culture to efavirenz have been obtained. The most frequently observed amino acid substitution in clinical trials with efavirenz is K103N (54%). One or more RT substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, 227, and 230 were observed in subjects failing treatment with efavirenz in combination with other antiretrovirals. Other resistance substitutions observed to emerge commonly included L100I (7%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%). HIV-1 isolates with reduced susceptibility to efavirenz (greater than 380-fold increase in EC90 value) emerged rapidly under selection in cell culture. Genotypic characterization of these viruses identified substitutions resulting in single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in RT.

Emtricitabine: Emtricitabine-resistant isolates of HIV-1 have been selected in cell culture and in clinical trials. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a substitution in the HIV-1 RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in RT and showed a 2- to 4-fold reduction in susceptibility to tenofovir.

Cross Resistance

Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate: Cross-resistance has been recognized among NNRTIs. Cross resistance has also been recognized among certain NRTIs. The M184V/I and/or K65R substitutions selected in cell culture by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

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

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility in cell culture to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine.

Tenofovir Disoproxil Fumarate: The K65R substitution selected by tenofovir is also selected in some HIV-1 infected patients treated with abacavir, didanosine, or zalcitabine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R substitution. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to tenofovir DF . Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 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. In studies in which rats were administered efavirenz at doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above background were observed. The systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans receiving the 600-mg/day dose. The exposure in rats was lower than that in humans. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, efavirenz showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. 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. Given the lack of genotoxic activity of efavirenz, the relevance to humans of neoplasms in efavirenz-treated mice is not known.

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.

As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

Emtricitabine: In long-term carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/day (31 times the human systemic exposure at the therapeutic dose).

Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays. Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth *(in utero)* through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

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

Tenofovir DF was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir DF was negative when administered to male mice. There were no effects on fertility, mating performance or early embryonic development when tenofovir DF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through Day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

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

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

Evidence of renal toxicity was noted in 4 animal species administered tenofovir and tenofovir DF. 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.

14 CLINICAL STUDIES

Clinical Study 934 supports the use of tenofovir DF/emtricitabine/efavirenz tablets in antiretroviral treatment-naive HIV-1 infected patients. Additional data in support of the use of tenofovir DF/emtricitabine/efavirenz in treatment naive patients can be found in the prescribing information for tenofovir DF.

Clinical Study 073 provides clinical experience in subjects with stable, virologic suppression and no history of virologic failure who switched from their current regimen to tenofovir DF/emtricitabine/efavirenz. In antiretroviral treatment-experienced patients, the use of tenofovir DF/emtricitabine/efavirenz tablets may be considered for patients with HIV-1 strains that are expected to be susceptible to the components of tenofovir DF/emtricitabine/efavirenz as assessed by treatment history or by genotypic or phenotypic testing *[See Clinical Pharmacology (12.4)].*

Study 934: Data through 144 weeks are reported for Study 934, a randomized, open label, active-controlled multicenter trial comparing emtricitabine + tenofovir DF administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naive subjects. From Weeks 96 to 144 of the trial, subjects received emtricitabine/tenofovir DF fixed-dose combination with efavirenz in place of emtricitabine + tenofovir DF with efavirenz. Subjects had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4+ cell count was 245 cells/mm3 (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 log10 copies/mL (range 3.56–6.54). Subjects were stratified by baseline CD4+ cell count (< or ≥200 cells/mm^3) and 41% had CD4+ cell counts <200 cells/mm^3. Fifty-one percent (51%) of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have efavirenz resistance at baseline (N=487) are presented in Table 9.

Table 9: Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144	
	FTC + TDF + EFV (N=244)	AZT/3TC + EFV (N=243)	FTC + TDF + EFV (N=227)[a]	AZT/3TC + EFV (N=229)[a]
Responder[b]	84%	73%	71%	58%
Virologic failure[c]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretoviral regimen	1%	1%	1%	1%
Death	<1%	1%	1%	1%
Discontinued due to adverse event	4%	9%	5%	12%
Discontinued for other reasons[d]	10%	14%	20%	22%

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue trial after Week 48 or Week 96 were excluded from analysis. b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144. c. Includes confirmed viral rebound and failure to achieve confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144. d. Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

Through Week 48, 84% and 73% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label trial. In addition, 80% and 70% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4+ cell count was 190 cells/mm3 in the emtricitabine + tenofovir DF group and 158 cells/mm3 in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm3 at Week 144).

Through 48 weeks, 7 subjects in the emtricitabine + tenofovir DF group and 5 subjects in the zidovudine/lamivudine group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

Study 073: Study 073 was a 48-week open-label, randomized clinical trial in subjects with stable virologic suppression on combination antiretroviral therapy consisting of at least two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a protease inhibitor (with or without ritonavir) or a non-nucleoside reverse transcriptase inhibitor (NNRTI).

To be enrolled, subjects were to have HIV-1 RNA <200 copies/mL for at least 12 weeks on their current regimen prior to trial entry with no known HIV-1 substitutions conferring resistance to the components of Trustiva and no history of virologic failure.

The trial compared the efficacy of switching to Trustiva or staying on the baseline antiretroviral regimen (SBR). Subjects were randomized in a 2:1 ratio to switch to Trustiva (N=203) or stay on SBR (N=97). Subjects had a mean age of 43 years (range 22-73 years), 88% were male, 68% were white, 29% were Black or African-American, and 3% were of other races. At baseline, median CD4+ cell count was 516 cells/mm3 and 96% had HIV-1 RNA <50 copies/mL. The median time since onset of antiretroviral therapy was 3 years and 88% of subjects were receiving their first antiretroviral regimen at trial enrollment.

At Week 48, 89% and 87% of subjects who switched to Trustiva maintained HIV RNA <200 copies/mL and <50 copies/mL, respectively, compared to 88% and 85% who remained on SBR; this difference was not statistically significant. No changes in CD4+ cell counts from baseline to Week 48 were observed in either treatment arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

Trustiva tablets are puff pinkish, capsule-shaped, film-coated, debossed with "128" on one side and "H" on the other side. Each bottle contains 30 tablets (NDC 15584- 0101-1) and silica gel desiccant, and is closed with a child-resistant closure.

Store at 25 °C

- Keep container tightly closed.
- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

17.1 Drug Interactions

A statement to patients and healthcare providers is included on the product's bottle labels: *ALERT: Find out about medicines that should NOT be taken with Trustiva.*

Trustiva may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort.

17.2 General Information for Patients

Patients should be advised that:

- Trustiva is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using Trustiva.
- Patients should avoid doing things that can spread HIV-1 to others.
- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Some of the medicines in Trustiva can be passed to your baby in your breast milk. We do not know whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.
- The long-term effects of Trustiva are unknown.
- Redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known.
- Trustiva should not be coadministered with emtricitabine/rilpivirine/tenofovir DF, emtricitabine, elvitegravir/cobicistat/emtricitabine/tenofovir DF, emtricitabine/tenofovir DF, or tenofovir DF ; or drugs containing lamivudine, including lamivudine/zidovudine, lamivudine, lamivudine-HBV, abacavir sulfate/lamivudine, or abacavir sulfate/lamivudine/zidovudine. efavirenz should not be coadministered with Trustiva unless needed for dose adjustment *[See Warnings and Precautions (5.4)].*
- Trustiva should not be administered with adefovir dipivoxil *[See Warnings and Precautions (5.2)].*

17.3 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Patients should be informed that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment will be suspended in any patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[See Warnings and Precautions (5.1)].*

17.4 Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for hepatitis B virus (HBV) before initiating antiretroviral therapy. Patients should be advised that severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, which are components of Trustiva.

17.5 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Trustiva should be avoided with concurrent or recent use of a nephrotoxic agent (e.g. high-dose or multiple NSAIDs) *[See Warnings and Precautions (5.7)].*

17.6 Decreases in Bone Mineral Density

Patients should be informed that decreases in bone mineral density have been observed with the use of tenofovir DF. Bone mineral density monitoring may be performed in patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss *[See Warnings and Precautions (5.11)].*

17.7 Dosing Instructions

Patients should be advised to take Trustiva orally on an empty stomach and that it is important to take Trustiva on a regular dosing schedule to avoid missing doses.

17.8 Nervous System Symptoms

Patients should be informed that central nervous system symptoms (NSS) including dizziness, insomnia, impaired concentration, drowsiness, and abnormal dreams are commonly reported during the first weeks of therapy with efavirenz. Dosing at bedtime may improve the tolerability of these symptoms, which are likely to improve with continued therapy. Patients should be alerted to the potential for additive effects when Trustiva is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience NSS they should avoid potentially hazardous tasks such as driving or operating machinery *[See Warnings and Precautions (5.6) and Dosage and Administration (2)].*

17.9 Psychiatric Symptoms

Patients should be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia, and psychosis-like symptoms have been reported in patients receiving efavirenz. If they experience severe psychiatric adverse experiences they should seek immediate medical evaluation. Patients should be advised to inform their physician of any history of mental illness or substance abuse *[See Warnings and Precautions (5.5)].*

17.10 Rash

Patients should be informed that a common side effect is rash. Rashes usually go away without any change in treatment. However, since rash may be serious, patients should be advised to contact their physician promptly if rash occurs.

17.11 Reproductive Risk Potential

Women receiving Trustiva should be instructed to avoid pregnancy *[See Warnings and Precautions (5.8)].* A reliable form of barrier contraception must always be used in combination with other methods of contraception, including oral or other hormonal contraception. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of Trustiva is recommended. Women should be advised to notify their physician if they become pregnant or plan to become pregnant while taking Trustiva. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential harm to the fetus.

Shelf Life

Refer the outer carton for the date of expiry. The date of expiry is the last day of the month.

Packaging information

Bottle Pack of 30 tablets

Storage and Handling Instructions

Store protected from moisture at a temperature not exceeding 30ºC.

Keep out of reach of children.

Dispense in original container.

Keep container tightly closed.

Mfg. Lic. No.: 405/DR/mfg/2017

Manufactured in India by:

HETERO HEALTHCARE LIMITED
AIIDC Industrial Growth Centre,
Changsari, Niz Sindurighopa (Village),
Sila Sindurighopa (Mouza),
Kamrup (Dist), Assam – 781101.

12003736