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EFAVIRENZ tablets for oral use

2050824

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EFAVIRENZ TABLETS safely and effectively. See full prescribing information for EFAVIRENZ TABLETS.

EFAVIRENZ tablets for oral use

Initial U.S. Approval: 1998

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Hepatic Function (2.1)	10/2017
Contraindications, Antiviral Agents (4)	10/2017
Warnings and Precautions, Psychiatric Symptoms (5.5)	01/2017
Warnings and Precautions, Hepatotoxicity (5.9)	10/2017

----------INDICATIONS AND USAGE----------

Efavirenz is a non-nucleoside reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 infection in adults and in pediatric patients atleast 3 months old and weighing at least 3.5 kg. (1)

----------DOSAGE AND ADMINISTRATION----------

- Efavirenz tablets should be taken orally once daily on an empty stomach, preferably at bedtime. (2)
- Recommended adult dose: 600 mg. (2.2)
- Pediatric dosing is based on weight. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 600 mg (3)

----------CONTRAINDICATIONS----------

- Patients with previously demonstrated hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4)
- Coadministration of efavirenz with elbasvir/grazoprevir.

----------WARNINGS AND PRECAUTIONS----------

- *QTc prolongation:* Consider alternatives to efavirenz in patients taking other medications with a known risk of Torsade de Pointes or in patients at higher risk of Torsade de Pointes. (5.2)
- *Do not use as a single agent* or add on as a sole agent to a failing regimen. Consider potential for cross-resistance when choosing other agents. (5.3)
- Not recommended with ATRIPLA, which contains efavirenz, emtricitabine, and tenofovir disoproxil fumarate, unless needed for dose adjustment when coadministered with rifampin. (5.4)
- *Serious psychiatric symptoms:* Immediate medical evaluation is recommended for serious psychiatric symptoms such as severe depression or suicidal ideation. (5.5, 17)
- *Nervous system symptoms* (NSS): NSS are frequent and usually begin 1 to 2 days after initiating therapy and resolve in 2 to 4 weeks. Dosing at bedtime may improve tolerability. NSS are not predictive of onset of psychiatric symptoms. (5.6, 6.1, 17)
- *Embryo-Fetal Toxicity:* Avoid administration in the first trimester of pregnancy as fetal harm may occur. (5.7, 8.1)
- *Hepatotoxicity:* Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B or C coinfection, marked transaminase elevations, or who are taking medications associated with liver toxicity. Among reported cases of hepatic failure, a few occurred in patients with no pre-existing hepatic disease. (5.9, 6.1, 8.6)
- *Rash:* Rash usually begins within 1 to 2 weeks after initiating therapy and resolves within 4 weeks. Discontinue if severe rash develops. (5.8, 6.1, 17)
- *Convulsions:* Use caution in patients with a history of seizures. (5.10)
- *Lipids:* Total cholesterol and triglyceride elevations. Monitor before therapy and periodically thereafter. (5.11)
- *Immune reconstitution syndrome:* May necessitate further evaluation and treatment. (5.12)
- *Redistribution/accumulation of body fat:* Observed in patients receiving antiretroviral therapy. (5.13, 17)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>5%, moderate-severe) are impaired concentration, abnormal dreams, rash, dizziness, nausea, headache, fatigue, insomnia, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Coadministration of efavirenz can alter the concentrations of other drugs and other drugs may alter the concentrations of efavirenz. The potential for drug-drug interactions should be considered before and during therapy. (7)

----------USE IN SPECIFIC POPULATIONS----------

- *Lactation:* Breastfeeding not recommended. (8.2)
- *Females and Males of Reproductive Potential:* Pregnancy testing and contraception are recommended. (8.3)
- *Hepatic impairment:* Efavirenz tablets are not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment. (8.6)
- *Pediatric patients:* The incidence of rash was higher than in adults. (5.8, 6.2, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Efavirenz tablets in combination with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients at least 3 months old and weighing at least 3.5 kg.

2 DOSAGE AND ADMINISTRATION

2.1 Hepatic Function

Monitor hepatic function prior to and during treatment with efavirenz tablets *[see Warnings and Precautions (5.9)]*.

Efavirenz tablets are not recommended in patients with moderate or severe hepatic impairment (Child Pugh B or C) *[see Warnings and Precautions (5.9) and Use in Specific Populationns (8.6)]*.

2.2 Adults

The recommended dosage of efavirenz tablets are 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs). It is recommended that efavirenz tablets be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration of efavirenz tablets with food may lead to an increase in frequency of adverse reactions [*see Clinical Pharmacology (12.3)*]. Dosing at bedtime may improve the tolerability of nervous system symptoms [*see Warnings and Precautions (5.6), Adverse Reactions (6.1),* and *Patient Counseling Information (17)*]. Efavirenz tablets should be swallowed intact with liquid.

Concomitant Antiretroviral Therapy

Efavirenz tablets must be given in combination with other antiretroviral medications [*see Indications and Usage (1), Warnings and Precautions (5.3), Drug Interactions (7.1),* and *Clinical Pharmacology (12.3)*].

2.3 Pediatric Patients

It is recommended that efavirenz tablets be taken on an empty stomach, preferably at bedtime. Table 1 describes the recommended dose of efavirenz tablets for pediatric patients 3 months of age or older and weighing between 3.5 kg and 40 kg *[see Clinical Pharmacology (12.3)]*. The recommended dosage of efavirenz tablets for pediatric patients weighing 40 kg or greater is 600 mg once daily.

Table 1: Efavirenz Tablets Dosing in Pediatric Patients

Patient Body Weight	Efavirenz Tablets Daily Dose	Number of Tablets[b] and Strength to Administer
at least 40 kg	600 mg	one 600 mg tablet

[b] Tablets must not be crushed.

3 DOSAGE FORMS AND STRENGTHS

- *Tablets*

600 mg tablets are yellow, capsular-shaped, film-coated tablets, with 'H' on one side and '4' on the other side.

4 CONTRAINDICATIONS

- Efavirenz tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.
- Coadministration of efavirenz with elbasvir and grazoprevir is contraindicated *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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. The most prominent effect of efavirenz at steady-state is induction of CYP3A and CYP2B6. [*See Dosage and Administration (2.2) and Drug Interactions (7.1).]*

5.2 QTc Prolongation

QTc prolongation has been observed with the use of efavirenz *[see Drug Interactions (7.3, 7.4) and Clinical Pharmacology (12.2)]*. Consider alternatives to efavirenz tablets when coadministered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes.

5.3 Resistance

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

5.4 Coadministration with Related Products

Coadministration of efavirenz tablets with ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg) is not recommended unless needed for dose adjustment (eg, with rifampin), since efavirenz is one of its active ingredients.

5.5 Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz tablets. In controlled trials of 1,008 patients treated with regimens containing efavirenz tablets for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among patients who received efavirenz tablets or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study 006, treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz tablets and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz tablets-treated and control-treated patients. One percent of efavirenz tablets-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions, psychosis-like behavior and catatonia, although a causal relationship to the use of efavirenz tablets cannot be determined from these reports. Postmarketing cases of catatonia have also been reported and may be associated with increased efavirenz exposure. 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 tablets, and if so, to determine whether the risks of continued therapy outweigh the benefits. *[See Adverse Reactions (6.1).]*

5.6 Nervous System Symptoms

Fifty-three percent (531/1,008) of patients receiving efavirenz tablets in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens [*see Adverse Reactions (6.1, Table 3)*]. These symptoms included, but were not limited to, dizziness (28.1% of the 1,008 patients), insomnia (16.3%), impaired concentration (8.3%), somnolence (7%), abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in 2% of patients, and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing efavirenz tablets and from 3% to 5% in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms [*see Warnings and Precautions (5.5)*]. 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 patients treated with efavirenz tablets + zidovudine + lamivudine, efavirenz tablets + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz tablets-treated patients were generally similar to those in the indinavir-containing control arm.

Patients receiving efavirenz tablets should be alerted to the potential for additive central nervous system effects when efavirenz tablets are 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 Embryo-Fetal Toxicity

Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Advise females of reproductive potential who are receiving efavirenz tablets to avoid pregnancy. [*See Use in Specific Populations (8.1 and 8.3).*]

5.8 Rash

In controlled clinical trials, 26% (266/1,008) of adult patients treated with 600 mg efavirenz tablets experienced new-onset skin rash compared with 17% (111/635) of those treated in control groups [*see Adverse Reactions (6.1)*]. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1,008) of patients treated with efavirenz tablets. The incidence of Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in adult patients treated with efavirenz tablets in all studies and expanded access was 0.1%. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in adult clinical trials was 1.7% (17/1,008).

Rash was reported in 59 of 182 pediatric patients (32%) treated with efavirenz tablets [*see Adverse Reactions (6.2)*]. Two pediatric patients experienced Grade 3 rash (confluent rash with fever, generalized rash), and four patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 28 days (range 3 to 1,642 days). Prophylaxis with appropriate antihistamines before initiating therapy with efavirenz tablets in pediatric patients should be considered.

Efavirenz tablets can generally be reinitiated in patients interrupting therapy because of rash. Efavirenz tablets should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. For patients who have had a life-threatening cutaneous reaction (eg, Stevens-Johnson syndrome), alternative therapy should be considered [*see also Contraindications (4.1)*].

5.9 Hepatotoxicity

Postmarketing cases of hepatitis, including fulminant hepatitis progressing to liver failure requiring transplantation or resulting in death, have been reported in patients treated with efavirenz. Reports have included patients with underlying hepatic disease, including coinfection with hepatitis B or C, and patients without pre-existing hepatic disease or other identifiable risk factors.

Efavirenz is not recommended for patients with moderate or severe hepatic impairment. Careful monitoring is recommended for patients with mild hepatic impairment receiving efavirenz. [*see Adverse Reactions (6.1)* and *Use in Specific Populations (8.6)*].

Monitoring of liver enzymes before and during treatment is recommended for all patients [*see Dosage and Administration (2.1)*]. Consider discontinuing efavirenz in patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range.

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

5.10 Convulsions

Convulsions have been observed in adult and pediatric patients receiving efavirenz, generally in the presence of known medical history of seizures [*see Nonclinical Toxicology (13.2)*]. Caution should be taken in any patient with a history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels [*see Drug Interactions (7.1)*].

5.11 Lipid Elevations

Treatment with efavirenz tablets has resulted in increases in the concentration of total cholesterol and triglycerides [*see Adverse Reactions (6.1)*]. Cholesterol and triglyceride testing should be performed before initiating efavirenz tablets therapy and at periodic intervals during therapy.

5.12 Immune Reconstitution Syndrome

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

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

5.13 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

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

- psychiatric symptoms [*see Warnings and Precautions (5.5)*],
- nervous system symptoms [*see Warnings and Precautions (5.6)*],
- rash [*see Warnings and Precautions (5.8)*].
- hepatotoxicity *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

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

Adverse Reactions in Adults

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

Selected clinical adverse reactions of moderate or severe intensity observed in ≥2% of efavirenz tablets-treated patients in two controlled clinical trials are presented in Table 2.

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

	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI-, and Protease Inhibitor-Naive Patients		
	Efavirenz tablets[b] + ZDV/LAM (n=412)	Efavirenz tablets[b] + Indinavir (n=415)	Indinavir + ZDV/LAM (n=401)	Efavirenz tablets[b] + Nelfinavir + NRTIs (n=64)	Efavirenz tablets[b] + NRTIs (n=65)	Nelfinavir + NRTIs (n=66)
Adverse Reactions	180 weeks[c]	102 weeks[c]	76 weeks[c]	71.1 weeks[c]	70.9 weeks[c]	62.7 weeks[c]
Body as a Whole						
Fatigue	8%	5%	9%	0	2%	3%
Pain	1%	2%	8%	13%	6%	17%
Central and Peripheral Nervous System						
Dizziness	9%	9%	2%	2%	6%	6%
Headache	8%	5%	3%	5%	2%	3%
Insomnia	7%	7%	2%	0	0	2%
Concentration impaired	5%	3%	<1%	0	0	0
Abnormal dreams	3%	1%	0	—	—	—
Somnolence	2%	2%	<1%	0	0	0
Anorexia	1%	<1%	<1%	0	2%	2%
Gastrointestinal						
Nausea	10%	6%	24%	3%	2%	2%
Vomiting	6%	3%	14%	—	—	—
Diarrhea	3%	5%	6%	14%	3%	9%
Dyspepsia	4%	4%	6%	0	0	2%
Abdominal pain	2%	2%	5%	3%	3%	3%
Psychiatric						
Anxiety	2%	4%	<1%	—	—	—
Depression	5%	4%	<1%	3%	0	5%
Nervousness	2%	2%	0	2%	0	2%
Skin & Appendages						
Rash[d]	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

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

[b] Efavirenz tablets provided as 600 mg once daily.

[c] Median duration of treatment.

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

— = Not Specified.

ZDV = zidovudine, LAM=lamivudine.

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

Nervous System Symptoms

For 1,008 patients treated with regimens containing efavirenz tablets and 635 patients treated with a control regimen in controlled trials, Table 3 lists the frequency of symptoms of different degrees of severity and gives the discontinuation rates for one or more of the following nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization [*see Warnings and Precautions (5.6)*]. The frequencies of specific central and peripheral nervous system symptoms are provided in Table 2.

Table 3: Percent of Patients with One or More Selected Nervous System Symptoms[a,b]

Percent of Patients with:	Efavirenz Tablets 600 mg Once Daily (n=1,008) %	Control Groups (n=635) %
Symptoms of any severity	52.7	24.6
Mild symptoms[c]	33.3	15.6
Moderate symptoms[d]	17.4	7.7
Severe symptoms[e]	2	1.3
Treatment discontinuation as a result of symptoms	2.1	1.1

[a] Includes events reported regardless of causality.

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

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

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

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

Psychiatric Symptoms

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

Rash

In controlled clinical trials, the frequency of rash (all grades, regardless of causality) was 26% for 1,008 adults treated with regimens containing efavirenz tablets and 17% for 635 adults treated with a control regimen. Most reports of rash were mild or moderate in severity. The frequency of Grade 3 rash was 0.8% for efavirenz tablets-treated patients and 0.3% for control groups, and the frequency of Grade 4 rash was 0.1% for efavirenz tablets and 0 for control groups. The discontinuation rates as a result of rash were 1.7% for efavirenz tablets-treated patients and 0.3% for control groups [*see Warnings and Precautions (5.8)*].

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

Laboratory Abnormalities

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

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

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

[a] Efavirenz tablets provided as 600 mg once daily.

[b] Median duration of treatment.

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

[d] Nonfasting.

ZDV = zidovudine, LAM = lamivudine, ULN = upper limit of normal, ALT = alanine aminotransferase,
AST = aspartate aminotransferase, GGT = gamma-glutamyltransferase.

Patients Coinfected with Hepatitis B or C

Liver function tests should be monitored in patients with a history of hepatitis B and/or C. In the long-term data set from Study 006, 137 patients treated with efavirenz tablets-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these coinfected patients, elevations in AST to greater than five times ULN developed in 13% of patients in the efavirenz tablets arms and 7% of those in the control arm, and elevations in ALT to greater than five times ULN developed in 20% of patients in the efavirenz tablets arms and 7% of patients in the control arm. Among coinfected patients, 3% of those treated with efavirenz tablets-containing regimens and 2% in the control arm discontinued from the study because of liver or biliary system disorders [*see Warnings and Precautions (5.9)*].

Lipids

Increases from baseline in total cholesterol of 10 to 20% have been observed in some uninfected volunteers receiving efavirenz. In patients treated with efavirenz tablets + zidovudine + lamivudine, increases from baseline in nonfasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with efavirenz tablets + indinavir, increases from baseline in nonfasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed. Nonfasting total cholesterol levels ≥240 mg/dL and ≥300 mg/dL were reported in 34% and 9%, respectively, of patients treated with efavirenz tablets + zidovudine + lamivudine; 54% and 20%, respectively, of patients treated with efavirenz tablets + indinavir; and 28% and 4%, respectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of efavirenz tablets on triglycerides and LDL in this study were not well characterized since samples were taken from nonfasting patients. The clinical significance of these findings is unknown [*see Warnings and Precautions (5.11)*].

Adverse Reactions in Pediatric Patients

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

Assessment of adverse reactions is based on three clinical trials in 182 HIV-1 infected pediatric patients (3 months to 21 years of age) who received efavirenz tablets in combination with other antiretroviral agents for a median of 123 weeks. The adverse reactions observed in the three trials were similar to those observed in clinical trials in adults except that rash was more common in pediatric patients (32% for all grades regardless of causality) and more often of higher grade (ie, more severe). Two (1.1%) pediatric patients experienced Grade 3 rash (confluent rash with fever, generalized rash), and four (2.2%) pediatric patients had Grade 4 rash (all erythema multiforme). Five pediatric patients (2.7%) discontinued from the study because of rash [*see Warnings and Precautions (5.8)*].

6.2 Postmarketing Experience

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

Body as a Whole: allergic reactions, asthenia, redistribution/accumulation of body fat [*see Warnings and Precautions (5.13)*]

Central and Peripheral Nervous System: abnormal coordination, ataxia, cerebellar coordination and balance disturbances, convulsions, hypoesthesia, paresthesia, neuropathy, tremor, vertigo

Endocrine: gynecomastia

Gastrointestinal: constipation, malabsorption

Cardiovascular: flushing, palpitations

Liver and Biliary System: hepatic enzyme increase, hepatic failure, hepatitis.

Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia

Musculoskeletal: arthralgia, myalgia, myopathy

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

Respiratory: dyspnea

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

Special Senses: abnormal vision, tinnitus

7 DRUG INTERACTIONS

7.1 Potential for Efavirenz to Affect other Drugs

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 tablets.

7.2 Potential for Other Drugs to Affect Efavirenz

Drugs that induce CYP3A activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations [*see Dosage and Administration (2.2)*].

7.3 QT Prolonging Drugs

There is limited information available on the potential for a pharmacodynamic interaction between efavirenz and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of efavirenz [*see Clinical Pharmacology (12.2)*]. Consider alternatives to efavirenz when coadministered with a drug with a known risk of Torsade de Pointes.

7.4 Established and Other Potentially Significant Drug Interactions

Drug interactions with efavirenz tablets are summarized in Tables 5. for pharmacokinetics data, *[see Clinical pharmacology (12.3)]* Tables 7 and 8. This tables includes potentially significant interactions, but is not all inclusive.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
HIV antiviral agents		
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir	Fosamprenavir (unboosted): Appropriate doses of the combinations with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz tablets are administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when efavirenz tablets are administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir*	*Treatment-naive patients:* When coadministered with efavirenz tablets, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and efavirenz tablets 600 mg (once daily on an empty stomach, preferably at bedtime). *Treatment-experienced patients:* Coadministration of efavirenz tablets and atazanavir is not recommended.
Protease inhibitor: Indinavir	↓ indinavir*	The optimal dose of indinavir, when given in combination with efavirenz tablets, is not known. Increasing the indinavir dose to 1,000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz tablets.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir*	Lopinavir/ritonavir once daily dosing is not recommended when coadministered with efavirenz tablets. The dose of lopinavir/ritonavir must be increased when coadministered with efavirenz tablets. See the lopinavir/ritonavir prescribing information for dose adjustments of lopinavir/ritonavir when coadministered with efavirenz in adult and pediatric patients.
Protease inhibitor: Ritonavir	↑ ritonavir* ↑ efavirenz*	Monitor for elevation of liver enzymes and for adverse clinical experiences (e.g., dizziness, nausea, paresthesia) when efavirenz tablet is coadministered with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir*	Appropriate doses of the combination of efavirenz tablets and saquinavir/ritonavir with respect to safety and efficacy have not been established.
NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. Efavirenz tablets should not be coadministered with other NNRTIs.
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc*	Refer to the full prescribing information for maraviroc for guidance on coadministration with efavirenz.
Hepatitis C antiviral agents		
Boceprevir	↓ boceprevir*	Concomitant administration of boceprevir with efavirenz tablet is not recommended because it may result in loss of therapeutic effect of boceprevir.
Elbasvir/Grazoprevir	↓ elbasvir ↓ grazoprevir	Coadministration of clopidogrel with elbasvir/grazoprevir is contraindicated *[see Contraindications (4)]* because it may lead to loss of virologic response to elbasvir/grazoprevir.
Pibrentasvir/Glecaprevir	↓ pibrentasvir ↓ glecaprevir	Coadministration of clopidogrel is not recommended because it may lead to reduced therapeutic effect of pibrentasvir/glecaprevir.
Simeprevir	↓ simeprevir * ↔efavirenz*	Concomitant administration of simprevir with efavirenz tablets is not recommended because it may result in loss of therapeutic effect of simeprevir.
Velpatasvir/ Sofosbuvir	↓ velpatasvir	Coadministration of efavirenz and sofosbuvir/velpatasvir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir.
Velpatasvir /Sofosbuvir /Voxilaprevir	velpatasvir sofosbuvir	Coadministration of efavirenz and sofosbuvir/velpatasvir/voxilaprevir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir/voxilaprevir.
Other agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin	Monitor INR and adjust warfarin dosage if necessary.
Anticonvulsants: Carbamazepine	↓ carbamazepine* ↓ efavirenz*	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants: Bupropion	↓ bupropion*	Increases in bupropion dosage should be guided by clinical response. Bupropion dose should not exceed the maximum recommended dose.
Sertraline	↓ sertraline*	Increases in sertraline dosage should be guided by clinical response.
Antifungals: Voriconazole	↓ voriconazole* ↑ efavirenz*	Efavirenz tablets and voriconazole should not be coadministered at standard doses. When voriconazole is coadministered with efavirenz tablets, voriconazole maintenance dose should be increased to 400 mg every 12 hours and efavirenz tablets dose should be decreased to 300 mg once daily using the capsule formulation. Efavirenz tablets must not be broken. [*See Dosage and Administration (2.1) and Clinical Pharmacology (12.3, Tables 7 and 8).*]
Itraconazole	↓ itraconazole* ↓ hydroxyitraconazole*	Consider alternative antifungal treatment because no dose recommendation for itraconazole can be made.
Ketoconazole	↓ ketoconazole	Consider alternative antifungal treatment because no dose recommendation for ketoconazole can be made.
Posaconazole	↓ posaconazole*	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ clarithromycin* ↑ 14-OH metabolite*	Consider alternatives to macrolide antibiotics because of the risk of QT interval prolongation.
Antimycobacterials: Rifabutin	↓ 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*	Increase efavirenz tablets to 800 mg once daily when coadministered with rifampin to patients weighing 50 kg or more.
Antimalarials: Artemether/ lumefantrine	↓ artemether* ↓ dihydroartemisinin* ↓ lumefantrine*	Consider alternatives to artemether/ lumefantrine because of the risk of QT interval prolongation.
Atovaquone/ proguanil	↓ atovaquone ↓ proguanil	Concomitant administration is not recommended.
Calcium channel blockers: Diltiazem	↓ diltiazem* ↓ desacetyl diltiazem* ↓ N-monodesmethyl diltiazem*	Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). No dose adjustment of efavirenz is necessary when administered with diltiazem.
Others (eg, felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	When coadministered with efavirenz tablets, dosage adjustment of calcium channels blocker may be needed and should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin* ↓ pravastatin* ↓ simvastatin*	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgestimate	↓ active metabolites of norgestimate*	A reliable method of barrier contraception should be used in addition to hormonal contraceptives.
Implant Etonogestrel	↓ etonogestrel	A reliable method of barrier contraception should be used in addition to hormonal contraceptives. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A	↓ immunosuppressant	Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz.
Narcotic analgesic: Methadone	↓ methadone*	Monitor for signs of methadone withdrawal and increase methadone dose if required to alleviate withdrawal symptoms.

* The interaction between efavirenz tablets and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.

This table is not all-inclusive.

7.5 Drugs Without Clinically Significant Interactions with Efavirenz

No dosage adjustment is recommended when efavirenz is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lorazepam, nelfinavir, nucleoside reverse transcriptase inhibitors (abacavir, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, zidovudine), paroxetine, and raltegravir.

7.6 Cannabinoid Test Interaction

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: *Teratogenic Effects*

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to efavirenz tablets during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263.

Risk Summary

There are retrospective case reports of neural tube defects in infants whose mothers were exposed to efavirenz -containing regimens in the first trimester of pregnancy. Prospective pregnancy data from the Antiretroviral Pregnancy Registry are not sufficient to adequately assess this risk. Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Although a causal relationship has not been established between exposure to efavirenz in the first trimester and neural tube defects, similar malformations have been observed in studies conducted in monkeys at doses similar to the human dose. In addition, fetal and embryonic toxicities occurred in rats, at a dose ten times less than the human exposure at recommended clinical dose. Because of the potential risk of neural tube defects, efavirenz should not be used in the first trimester of pregnancy. Advise pregnant women of the potential risk to a fetus.

Data

Human Data

There are retrospective postmarketing reports of findings consistent with neural tube defects, including meningomyelocele, all in infants of mothers exposed to efavirenz-containing regimens in the first trimester.

Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of approximately 1,000 live births following exposure to efavirenz-containing regimens (including over 800 live births exposed in the first trimester), there was no difference between efavirenz and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program. As of the interim APR report issued December 2014, the prevalence of birth defects following first-trimester exposure was 2.3% (95% CI: 1.4% to 3.6%). One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported. This case also included severe oblique facial clefts and amniotic banding, which have a known association with anophthalmia.

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 of 20 fetuses/infants had one or more malformations; there were no malformed fetuses or infants from placebo-treated mothers. The malformations that occurred in these three monkey fetuses included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in a second, and cleft palate in the third. There was no NOAEL (no observable adverse effect level) established for this study because only one dosage was evaluated. In rats, efavirenz was administered either during organogenesis (gestation days 7 to 18) or from gestation day 7 through lactation day 21 at 50, 100, or 200 mg/kg/day. Administration of 200 mg/kg/day in rats was associated with increase in the incidence of early resorptions; and doses 100 mg/kg/day and greater were associated with early neonatal mortality. The AUC at the NOAEL (50 mg/kg/day) in this rat study was 0.1 times that in humans at the recommended clinical dose. Drug concentrations in the milk on lactation day 10 were approximately 8 times higher than those in maternal plasma. In pregnant rabbits, efavirenz was neither embryo lethal nor teratogenic when administered at doses of 25, 50, and 75 mg/kg/day over the period of organogenesis (gestation days 6 through 18). The AUC at the NOAEL (75 mg/kg/day) in rabbits was 0.4 times that in humans at the recommended clinical dose.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Because of the potential for HIV transmission in breastfed infants, advise women not to breastfeed.

8.3 Females and Males of Reproductive Potential

Because of potential teratogenic effects, pregnancy should be avoided in women receiving efavirenz tablets. [*See Use in Specific Populations (8.1).*]

Pregnancy Testing

Females of reproductive potential should undergo pregnancy testing before initiation of efavirenz tablets.

Contraception

Females of reproductive potential should use effective contraception during treatment with efavirenz tablets and for 12 weeks after discontinuing efavirenz tablets due to the long half-life of efavirenz. Barrier contraception should always be used in combination with other methods of contraception. Hormonal methods that contain progesterone may have decreased effectiveness [*see Drug Interactions (7.1)*].

Patient Information
Efavirenz (EF-a-VIR-enz)
Tablets USP

Important: Ask your doctor or pharmacist about medicines that should not be taken with efavirenz tablets. For more information, see the section "**What should I tell my doctor before taking efavirenz tablets?**"

Read this Patient Information before you start taking efavirenz tablets and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

What are efavirenz tablets?

Efavirenz tablets are a prescription HIV-1 (Human Immunodeficiency Virus type 1) medicine used with other antiretroviral medicines to treat HIV-1 infection in adults and in children who are at least 3 months old and who weigh at least 7 pounds 12 ounces (3.5 kg). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

It is not known if efavirenz tablets are safe and effective in children younger than 3 months of age or who weigh less than 7 pounds 12 ounces (3.5 kg).

When used with other antiretroviral medicines to treat HIV-1 infection, efavirenz tablets may help:

- reduce the amount of HIV-1 in your blood. This is called viral load.
- increase the number of CD4+ (T) cells in your blood that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

Efavirenz tablets does not cure HIV-1 infection or AIDS. You should keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others :

- Do not share or reuse 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 safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Ask your doctor if you have any questions about how to prevent passing HIV to other people.

Who should not take efavirenz tablets?

Do not take efavirenz tablets if you are allergic to efavirenz or any of the ingredients in efavirenz tablets. See the end of this leaflet for a complete list of ingredients in efavirenz tablets.

Do not take efavirenz if you are currently taking elbasvir and grazoprevir (zepatier®).

What should I tell my doctor before taking efavirenz tablets?

Before taking efavirenz tablets, tell your doctor if you have any medical conditions and in particular, if you:

- have a heart condition
- have ever had a mental health problem
- have ever used street drugs or large amounts of alcohol
- have liver problems, including hepatitis B or C virus infection
- have a history of seizures
- are pregnant or plan to become pregnant. Efavirenz tablets may harm your unborn baby. If you are able to become pregnant your healthcare provider should do a pregnancy test before you start efavirenz tablets. You should not become pregnant while taking efavirenz tablets and for 12 weeks after stopping treatment with efavirenz tablets.

Females who are able to become pregnant should use 2 effective forms of birth control during treatment and for 12 weeks after stopping treatment with efavirenz tablets. A barrier form of birth control should always be used along with another type of birth control.

- Barrier forms of birth control may include latex or polyurethane condom, contraceptive sponge, diaphragm with spermicide, and cervical cap.
- **Hormonal forms of birth control, such as birth control pills, injections, vaginal rings, or implants may not work during treatment with efavirenz tablets.**
- Talk to your doctor about forms of birth control that may be used during treatment with efavirenz tablets.
- **Pregnancy Registry.** There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.
- **Do not breastfeed if you take efavirenz tablets.**
- You should not breastfeed if you have HIV because of the risk of passing HIV to your baby.

Tell your doctor and pharmacist about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Efavirenz tablets may affect the way other medicines work, and other medicines may affect how efavirenz tablets works, and may cause serious side effects. If you take certain medicines with efavirenz tablets, the amount of efavirenz tablets in your body may be too low and it may not work to help control your HIV infection. The HIV virus in your body may become resistant to efavirenz tablets or other HIV medicines that are like it.

You should not take efavirenz tablets if you take ATRIPLA (efavirenz, emtricitabine, tenofovir disoproxil fumarate) unless your doctor tells you to.

Tell your doctor and pharmacist about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines interact with efavirenz tablets.

Keep a list of your medicines to show your doctor and pharmacist.

- You can ask your doctor or pharmacist for a list of medicines that interact with efavirenz tablets.
- **Do not start taking a new medicine without telling your doctor.** Your doctor can tell you if it is safe to take efavirenz tablets with other medicines.

How should I take efavirenz tablets?

- Take efavirenz tablets exactly as your doctor tells you to.
- Do not change your dose or stop taking efavirenz tablets unless your doctor tells you to.
- Stay under the care of your doctor during treatment with efavirenz tablets.
- Efavirenz tablets must be used with other antiretroviral medicines.
- Take efavirenz tablets 1 time each day.
- Efavirenz comes as tablets.
- Efavirenz tablets must not be broken.
- Swallow efavirenz tablets whole with liquid.

How and when to take efavirenz tablets.

- You should take efavirenz tablets on an empty stomach at bedtime. Taking efavirenz tablets with food increases the amount of medicine in your body. Some side effects may bother you less if you take efavirenz tablets on an empty stomach and at bedtime.
- Your child's doctor will prescribe the right dose of efavirenz tablets based on your child's weight.
- If you have difficulty swallowing tablets, tell your doctor.
- Do not miss a dose of efavirenz tablets. If you forget to take efavirenz tablets, take the missed dose right away, unless it is almost time for your next dose. Do not take 2 doses at one time. Just take your

Size : 400 x 680 mm
Book Folding : 35 x 35 mm
Spec: Printed on 40 GSM Bible paper, front & back side printing.

Color : Black
Pharma Code: 6974 6975

Note: 2D Barcode to be overprinting at supplier end & it contains our item code, supplier serial number.

8.4 Pediatric Use

The safety, pharmacokinetic profile, and virologic and immunologic responses of efavirenz tablets were evaluated in antiretroviral-naive and -experienced HIV-1 infected pediatric patients 3 months to 21 years of age in three open-label clinical trials [*see Adverse Reactions (6.2), Clinical Pharmacology (12.3), and Clinical Studies (14.2)*]. The type and frequency of adverse reactions in these trials were generally similar to those of adult patients with the exception of a higher frequency of rash, including a higher frequency of Grade 3 or 4 rash, in pediatric patients compared to adults [*see Warnings and Precautions (5.8) and Adverse Reactions (6.2)*].

Use of efavirenz tablets in patients younger than 3 months of age OR less than 3.5 kg body weight is not recommended because the safety, pharmacokinetics, and antiviral activity of efavirenz tablets have not been evaluated in this age group and there is a risk of developing HIV resistance if efavirenz tablets are underdosed. See *Dosage and Administration (2.2)* for dosing recommendations for pediatric patients.

8.5 Geriatric Use

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

8.6 Hepatic Impairment

Efavirenz tablets are not recommended for patients with moderate or severe hepatic impairment because there are insufficient data to determine whether dose adjustment is necessary. Patients with mild hepatic impairment may be treated with efavirenz without any adjustment in dose. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering efavirenz tablets to these patients [*see Warnings and Precautions (5.9)* and *Clinical Pharmacology (12.3)*].

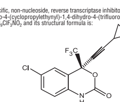
10 OVERDOSAGE

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

Treatment of overdose with efavirenz tablets should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with efavirenz tablets. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

11 DESCRIPTION

Efavirenz is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Efavirenz USP is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one. Its empirical formula is $C_{14}H_9ClF_3NO_2$ and its structural formula is:



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

Tablets: Efavirenz are available as film-coated tablets for oral administration containing 600 mg of efavirenz USP and the following inactive ingredients: microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate. The film coating contains Opadry® Yellow (hypromellose, titanium dioxide, iron oxide yellow and polyethylene glycol)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Efavirenz is an antiviral drug [*see Microbiology (12.4)*].

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of efavirenz on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

Absorption

Peak efavirenz plasma concentrations of 1.6 to 9.1 μM were attained by 5 hours following single oral doses of 100 mg to 1,600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1,600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

In HIV-1-infected patients at steady state, mean C_{max}, mean C_{min}, and mean AUC were dose proportional following 200 mg, 400 mg, and 600 mg daily doses. Time-to-peak plasma concentrations were approximately 3 to 5 hours and steady-state plasma concentrations were reached in 6 to 10 days. In 35 patients receiving efavirenz tablets 600 mg once daily, steady-state C_{max} was 12.9 ± 3.7 μM (mean ± SD), steady-state C_{min} was 5.6 ± 3.2 μM, and AUC was 184 ± 73 μM•h.

Effect of Food on Oral Absorption:

Tablets: Administration of a single 600 mg efavirenz tablet with a high-fat/high-caloric meal (approximately 1,000 kcal, 500 to 600 kcal from fat) was associated with a 28% increase in mean AUC_∞ of efavirenz and a 79% increase in mean C_{max} of efavirenz relative to the exposures achieved under fasted conditions. [*See Dosage and Administration (2)* and *Patient Counseling Information (17).*]

Distribution

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

Metabolism

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

Efavirenz has been shown to induce CYP enzymes, resulting in the induction of its own metabolism. Multiple doses of 200 to 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 to 42% lower) and a shorter terminal half-life of 40 to 55 hours (single dose half-life 52 to 76 hours).

Elimination

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

Special Populations

Pediatric: The pharmacokinetic parameters for efavirenz at steady state in pediatric patients were predicted by a population pharmacokinetic model.

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

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

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

Drug Interaction Studies

Efavirenz has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A and CYP2B6. *In vitro* studies have shown that efavirenz inhibited CYP isozymes 2C9 and 2C19 with K_i values (8.5 to 17 μM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82 to 160 μM) only at concentrations well above those achieved clinically. Coadministration of efavirenz with drugs primarily metabolized by CYP2C9, CYP2C19, CYP3A or CYP2B6 isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A and CYP2B6 activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Drug interaction studies were performed with efavirenz and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of efavirenz on the C_{max}, AUC, and C_{min} are summarized in Table 7 (effect of efavirenz on other drugs) and Table 8 (effect of other drugs on efavirenz). For information regarding clinical recommendations see *Drug Interactions (7.1)*.

Table 7: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓ 59% (49-67%)	↓ 74% (68-78%)	↓ 93% (90-95%)
	400 mg qd d 1-6, then 300 mg qd d 7-20 with ritonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7-20	13	↑ 14%[a] (↓17 -↑ 58%)	↑ 39%[a] (2- 88%)	↑ 48%[a] (24-76%)
	300 mg qd/ritonavir 100 mg qd d 1-10 (pm), then 400 mg qd/ritonavir100 mg qd d 11-24 (pm) (simultaneous with efavirenz)	600 mg qd with a light snack d 11-24 (pm)	14	↑ 17% (8-27%)	↔	↓ 42% (31-51%)
Indinavir	1,000 mg q8h x 10 days	600 mg qd x 10 days	20			
	After morning dose			↔[b]	↓ 33%[b] (26-39%)	↓ 39%[b] (24-51%)
	After afternoon dose			↔[b]	↓ 37%[b] (26-46%)	↓ 52%[b] (47-57%)
	After evening dose			↓ 29%[b] (11-43%)	↓ 46%[b] (37-54%)	↓ 57%[b] (50-63%)
Lopinavir/ ritonavir	400/100 mg capsules q12h x 9 days	600 mg qd x 9 days	11,7[c]	↔[d]	↓ 19%[d] (↓ 36-↑3%)	↓ 39%[d] (3-62%)
	500/125 mg tablet q12h x 10 days with efavirenz compared to 400/100 mg q12h alone	600 mg qd x 9 days	19	↑12%[d] (2-23%)	↔[d]	↓ 10%[d] (↓ 22-↑ 4%)
	600/150 mg tablet q12h x 10 days with efavirenz compared to 400/100 mg q12 h alone	600 mg qd x 9 days	23	↑ 36%[d] (28-44%)	↑ 36%[d] (28-44%)	↑ 32%[d] (21-44%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↑ 21% (10-33%)	↑ 20% (8-34%)	↔
Metabolite AG-1402				↓ 40% (30-48%)	↓ 37% (25-48%)	↓ 43% (21-59%)
Ritonavir	500 mg q12h × 8 days	600 mg qd × 10 days	11			
	After AM dose			↑ 24% (12-38%)	↑ 18% (6-33%)	↑ 42% (9-86%)[e]
	After PM dose			↔	↔	↑ 24% (3-50%)[e]
Saquinavir SGC[f]	1,200 mg q8h x 10 days	600 mg qd x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%)[e]
Lamivudine	150 mg q12h x 14 days	600 mg qd x 14 days	9	↔	↔	↑ 265% (37-873%)
Tenofovir[g]	300 mg qd	600 mg qd x 14 days	29	↔	↔	↔
Zidovudine	300 mg q12h x 14 days	600 mg qd x 14 days	9	↔	↔	↑ 225% (43-640%)
Maraviroc	100 mg bid	600 mg qd	12	↓ 51% (37-62%)	↓ 45% (38-51%)	↓ 45% (28-57%)
Raltegravir	400 mg single dose	600 mg qd	9	↓ 36% (2-59%)	↓ 36% (20-48%)	↓ 21% (↓ 51-↑ 28%)
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↓ 8% (↓ 22-↑ 8%)	↓ 19% (11-25%)	↓ 44% (26-58%)
Simeprevir	150 mg qd x 14 days	600 mg qd x 14 days	23	↓ 51% (↓ 46-↓56%)	↓ 71% (↓67-↓74%)	↓ 91% (↓88-↓92%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↑ 22% (4-42%)	↔	NA
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	11	↓ 26% (15-35%)	↓ 39% (30-46%)	↓ 53% (42-63%)
14-OH metabolite				↑ 49% (32-69%)	↑ 34% (18-53%)	↑ 26% (9-45%)
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↔	↔
Itraconazole	200 mg q12h x 28 days	600 mg qd x 14 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hydroxy-itraconazole				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg qd x 10 and 20 days	11	↓ 45% (34-53%)	↓ 50% (40-57%)	NA
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	9	↓ 32% (15-46%)	↓ 38% (28-47%)	↓ 45% (31-56%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↓ 61%[h]	↓ 77%[h]	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 36%[i] (21-49%)	↓ 55%[i] (45-62%)	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 23%[i] (↓ 1 - ↑ 53%)	↓ 7%[i] (↓ 23 -↑ 13%)	NA
Artemether/ lumefantrine	Artemether 20 mg/lumefantrine 120 mg tablets (64-tablet doses over 3 days)	600 mg qd × 26 days	12			
Arthemether				↓ 21%	↓ 51%	NA
dihydroartemisinin				↓ 38%	↓ 46%	NA
lumefantrine				↔	↓ 21%	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↓ 14% (1-26%)	↓ 43% (34-50%)	↓ 69% (49-81%)
Total active (including metabolites)				↓ 15% (2-26%)	↓ 32% (21-41%)	↓ 48% (23-64%)
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	13	↓ 32% (↓ 59-↑12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 72% (63-79 %)	↓ 68% (62-73 %)	↓45% (20-62%)
Total active (including metabolites)				↓ 68 % (55-78 %)	↓ 60 % (52-68 %)	NA[j]
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% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)
Epoxide metabolite				↔	↔	↓ 13% (↓ 30-↑7%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↓ 24% (18-30%)	↔	NA
Diltiazem	240 mg x 21 days	600 mg qd x 14 days	13	↓ 60% (50-68%)	↓ 69% (55-79%)	↓ 63% (44-75%)
Desacetyl diltiazem				↓ 64% (57-69%)	↓ 75% (59-84%)	↓ 62% (44-75%)
N-monodes-methyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol/ Norgestimate	0.035 mg/0.25 mg x 14 days	600 mg qd x 14 days				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromin			21	↓ 46% (39-52%)	↓ 64% (62-67%)	↓ 82% (79-85%)
Levonorgestrel			6	↓ 80% (77-83%)	↓ 83% (79-87%)	↓ 86% (80-90%)
Lorazepam	2 mg single dose	600 mg qd x 10 days	12	↑ 16% (2-32%)	↔	NA
Methadone	Stable maintenance 35-100 mg daily	600 mg qd x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Bupropion	150 mg single dose (sustained-release)	600 mg qd x 14 days	13	↓ 34% (21-47%)	↓ 55% (48-62%)	NA
Hydroxy-bupropion				↑ 50% (20-80%)	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	16	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↓ 29% (15-40%)	↓ 39% (27-50%)	↓ 46% (31-58%)

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

[a] Compared with atazanavir 400 mg qd alone.

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

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

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

[e] 95% CI.

[f] Soft Gelatin Capsule.

[g] Tenofovir disoproxil fumarate.

[h] 90% CI not available.

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

[j] Not available because of insufficient data.

NA = not available.

Table 8: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
Indinavir	800 mg q8h x 14 days	200 mg qd x 14 days	11	↔	↔	↔
Lopinavir/ritonavir	400/100 mg q12h x 9 days	600 mg qd x 9 days	11,12[a]	↔	↓ 16% (↓38-↑15%)	↓16% (↓42-↑20%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↓ 12% (↓32-↓13%)[b]	↓ 12% (↓35-↑18%)[b]	↓ 21% (↓53-↑33%)
Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)	↑ 25% (7-46%)[b]
Saquinavir SGC[c]	1,200 mg q8h x 10 days	600 mg qd x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%)[b]
Tenofovir[d]	300 mg qd	600 mg qd x 14 days	30	↔	↔	↔
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↑ 11% (2-20%)	↑ 20% (15-26%)	NA
simeprevir	150 mg qd x 14 days	600 mg qd x 14 days	23	↔	↓ 10% (5-15%)	↓13% (7-↑19%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↔	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	12	↑ 11% (3-19%)	↔	↔
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
Itraconazole	200 mg q12h x 14 days	600 mg qd x 28 days	16	↔	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	11	↔	↔	↓ 12% (↓ 24-↑1%)
Rifampin	600 mg x 7 days	600 mg qd x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↑ 38%[e]	↑44%[e]	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↑ 14%[f] (7-21%)	↔[f]	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↔[f]	↑17%[f] (6-29%)	NA
Artemether/ Lumefantrine	Artemether 20 mg/ lumefantrine 120 mg tablets (6 4-tablet doses over 3 days)	600 mg qd x 26 days	12	↔	↓ 17%	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↔	↔	↔
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	11	↔	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 12% (↓ 28-↑ 8%)	↔	↓ 12% (↓ 25-↑ 3%)
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days	600 mg qd x 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↔	↔	↔
Diltiazem	240 mg x 14 days	600 mg qd x 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	12	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↑ 11% (6-16%)	↔	↔

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

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

[b] 95% CI.

[c] Soft Gelatin Capsule.

[d] Tenofovir disoproxil fumarate.

[e] 90% CI not available.

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

NA = not available.

12.4 Microbiology

Mechanism of Action

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

Antiviral Activity in Cell Culture

The concentration of efavirenz inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90 to 95% ($EC_{90\ to\ 95}$) ranged from 1.7 to 25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/ monocyte cultures. Efavirenz demonstrated antiviral activity against clade B and most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses. Efavirenz demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine and nevirapine, NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. Efavirenz demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. Efavirenz was not antagonistic with adefovir, used for the treatment of hepatitis B virus infection, or ribavirin, used in combination with interferon for the treatment of hepatitis C virus infection.

Resistance

In cell culture

In cell culture, HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in EC_{90} value) emerged rapidly in the presence of drug. Genotypic characterization of these viruses identified single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in reverse transcriptase.

Clinical studies

Clinical isolates with reduced susceptibility in cell culture to efavirenz have been obtained. One or more substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, and 227 in reverse transcriptase were observed in patients failing treatment with efavirenz in combination with indinavir, or with zidovudine plus lamivudine. The K103N substitution was the most frequently observed. Long-term resistance surveillance (average 52 weeks, range 4 to 106 weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one percent (17/28) of these failure isolates had decreased efavirenz susceptibility in cell culture with a median 88-fold change in efavirenz susceptibility (EC_{50} value) from reference. The most frequent NNRTI substitution to develop in these patient isolates was K103N (54%). Other NNRTI substitutions that developed included L100I (7%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%).

Cross-Resistance

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

13.2 Animal Toxicology

Nonsustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose [*see Warnings and Precautions (5.10)*].

14 CLINICAL STUDIES

14.1 Adults

Study 006, a randomized, open-label trial, compared efavirenz tablets (600 mg once daily) + zidovudine (ZDV, 300 mg q12h) + lamivudine (LAM, 150 mg q12h) or efavirenz tablets (600 mg once daily) + indinavir (IDV, 1,000 mg q8h) with indinavir (800 mg q8h) + zidovudine (300 mg q12h) + lamivudine (150 mg q12h). Twelve hundred sixty-six patients (mean age 36.5 years [range 18 to 81], 60% Caucasian, 83% male) were enrolled. All patients were efavirenz-, lamivudine-, NNRTI-, and PI-naive at study entry. The median baseline CD4+ cell count was 320 cells/mm³ and the median baseline HIV-1 RNA level was 4.8 log_{10} copies/mL. Treatment outcomes with standard assay (assay limit 400 copies/mL) through 48 and 168 weeks are shown in Table 9. Plasma HIV RNA levels were quantified with standard (assay limit 400 copies/mL) and ultrasensitive (assay limit 50 copies/mL) versions of the AMPLICOR HIV-1 MONITOR assay. During the study, version 1.5 of the assay was introduced in Europe to enhance detection of non-clade B virus.

Table 9: Outcomes of Randomized Treatment Through 48 and 168 Weeks, Study 006

Outcome	Efavirenz tablets + ZDV + LAM (n=422) Week 48	Week 168	Efavirenz tablets + IDV (n=429) Week 48	Week 168	IDV + ZDV + LAM (n=415) Week 48	Week 168
Responder[a]	69%	48%	57%	40%	50%	29%
Virologic failure[b]	6%	12%	15%	20%	13%	19%
Discontinued for adverse events	7%	8%	6%	8%	16%	20%
Discontinued for other reasons[c]	17%	31%	22%	32%	21%	32%
CD4+ cell count (cells/mm³)						
Observed subjects (n)	(279)	(205)	(256)	(158)	(228)	(129)
Mean change from baseline	190	329	191	319	180	329

[a] Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 or Week 168.

[b] Includes patients who rebounded, patients who were on study at Week 48 and failed to achieve confirmed HIV-1 RNA <400 copies/mL at time of discontinuation, and patients who discontinued due to lack of efficacy.

[c] Includes consent withdrawn, lost to follow-up, noncompliance, never treated, missing data, protocol violation, death, and other reasons. Patients with HIV-1 RNA levels <400 copies/mL who chose not to continue in the voluntary extension phases of the study were censored at date of last dose of study medication.

For patients treated with efavirenz tablets + zidovudine + lamivudine, efavirenz tablets + indinavir, or indinavir + zidovudine + lamivudine, the percentage of responders with HIV-1 RNA<50 copies/mL was 65%, 50%, and 45%, respectively, through 48 weeks, and 43%, 31%, and 23%, respectively, through 168 weeks. A Kaplan-Meier analysis of time to loss of virologic response (HIV RNA <400 copies/mL) suggests that both the trends of virologic response and differences in response continue through 4 years.

ACTG 364 is a randomized, double-blind, placebo-controlled, 48-week study in NRTI-experienced patients who had completed two prior ACTG studies. One-hundred ninety-six patients (mean age 41 years [range 18 to 76], 74% Caucasian, 88% male) received NRTIs in combination with efavirenz tablets (600 mg once daily), or nelfinavir (NFV, 750 mg three times daily), or efavirenz tablets (600 mg once daily) + nelfinavir in a randomized, double-blinded manner. The mean baseline CD4+ cell count was 389 cells/mm³ and mean baseline HIV-1 RNA level was 8,130 copies/mL. Upon entry into the study, all patients were assigned a new open-label NRTI regimen, which was dependent on their previous NRTI treatment experience. There was no significant difference in the mean CD4+ cell count among treatment groups; the overall mean increase was approximately 100 cells at 48 weeks among patients who continued on study regimens. Treatment outcomes are shown in Table 10. Plasma HIV RNA levels were quantified with the AMPLICOR HIV-1 MONITOR assay using a lower limit of quantification of 500 copies/mL.

Table 10: Outcomes of Randomized Treatment Through 48 Weeks, Study ACTG 364*

Outcome	Efavirenz tablets + NFV + NRTIs (n=65)	Efavirenz tablets + NRTIs (n=65)	NFV +NRTIs (n=66)
HIV-1 RNA <500 copies/mL[a]	71%	63%	41%
HIV-1 RNA ≥500 copies/mL[b]	17%	34%	54%
CDC category C Event	2%	0%	0%
Discontinuations for adverse events[c]	3%	3%	5%
Discontinuations for other reasons[d]	8%	0%	0%

* For some patients, Week 56 data were used to confirm the status at Week 48.

[a] Subjects achieved virologic response (two consecutive viral loads <500 copies/mL) and maintained it through Week 48.

[b] Includes viral rebound and failure to achieve confirmed <500 copies/mL by Week 48.

[c] See *Adverse Reactions (6.1)* for a safety profile of these regimens.

[d] Includes loss to follow-up, consent withdrawn, noncompliance.

A Kaplan-Meier analysis of time to treatment failure through 72 weeks demonstrates a longer duration of virologic suppression (HIV RNA <500 copies/mL) in the efavirenz tablets-containing treatment arms.

14.2 Pediatric Patients

Study AI266922 is an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz in combination with didanosine and emtricitabine in antiretroviral-naive and -experienced pediatric patients. Thirty-seven patients 3 months to 6 years of age (median 0.7 years) were treated with efavirenz. At baseline, median plasma HIV-1 RNA was 5.88 log_{10} copies/mL, median CD4+ cell count was 1,144 cells/mm³, and median CD4+ percentage was 25%. The median time on study therapy was 60 weeks; 27% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (21/37) and 46% (17/37), respectively. The median increase from baseline in CD4+ count at 48 weeks was 196 cells/mm³ and the median increase in CD4+ percentage was 6%.

Study PACTG 1,021 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz in combination with didanosine and emtricitabine in pediatric patients who were antiretroviral therapy naive. Forty-three patients 3 months to 21 years of age (median 9.6 years) were dosed with efavirenz tablets. At baseline, median plasma HIV-1 RNA was 4.8 log_{10} copies/mL, median CD4+ cell count was 367 cells/mm³, and median CD4+ percentage was 18%. The median time on study therapy was 181 weeks; 16% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 77% (33/43) and 70% (30/43), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 238 cells/mm³ and the median increase in CD4+ percentage was 13%.

Study PACTG 382 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz in combination with nelfinavir and an NRTI in antiretroviral-naive and NRTI-experienced pediatric patients. One hundred two patients 3 months to 16 years of age (median 5.7 years) were treated with efavirenz tablets. Eighty-seven percent of patients had received prior antiretroviral therapy. At baseline, median plasma HIV-1 RNA was 4.57 log_{10} copies/mL, median CD4+ cell count was 755 cells/mm³, and median CD4+ percentage was 30%. The median time on study therapy was 118 weeks; 25% of patients discontinued before Week 48. Using an ITT analysis, the overall proportion of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (58/102) and 43% (44/102), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 128 cells/mm³ and the median increase in CD4+ percentage was 5%.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.2 Tablets

Efavirenz tablets, USP are available as follows:

Tablets 600 mg are yellow, capsular-shaped, film-coated tablets debossed with 'H' on one side and '4' on the other side.

Bottles of 30	NDC 31722-504-30
Bottles of 250	NDC 31722-504-25

16.3 Storage

Efavirenz tablets, USP should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

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 efavirenz tablets.

Efavirenz may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription or nonprescription medication.

General Information for Patients

Patients should be informed that efavirenz tablets are 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 while taking efavirenz tablets.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share or re-use 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 safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in breast milk.

Dosing Instructions

Patients should be advised to take efavirenz tablets every day as prescribed. If a patient forgets to take efavirenz tablets, tell the patient to take the missed dose right away, unless it is almost time for the next dose. Advise the patient not to take 2 doses at one time and to take the next dose at the regularly scheduled time. Advise the patient to ask a healthcare provider if he/she needs help in planning the best times to take his/her medicine.

Efavirenz tablets must always be used in combination with other antiretroviral drugs. Patients should be advised to take efavirenz tablets on an empty stomach, preferably at bedtime. Taking efavirenz tablets with food increases efavirenz concentrations and may increase the frequency of adverse reactions. Dosing at bedtime may improve the tolerability of nervous system symptoms [*see Dosage and Administration (2)* and *Adverse Reactions (6.1)*]. Healthcare providers should assist parents or caregivers in determining the best efavirenz tablets dosing schedule for infants and young children.

Patients should call their healthcare provider or pharmacist if they have any questions.

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 tablets [*see Warnings and Precautions (5.6)*]. 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 efavirenz tablets are 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.

Psychiatric Symptoms

Patients should be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia, and psychosis-like symptoms and catatonia have been reported in patients receiving efavirenz tablets [*see Warnings and Precautions (5.5)*]. 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.

Rash

Patients should be informed that a common side effect is rash [*see Warnings and Precautions (5.8)*]. 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.

Hepatotoxicity

Inform patients to watch for early warning signs of liver inflammation or failure, such as fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice, confusion, abdominal swelling, and discolored feces, and to consult their health care professional without delay if such symptoms occur *[see warnings and precautions (5.9) and adverse Reactions (6.1)]*.

Females of Reproductive Potential

Advise females of reproductive potential to use effective contraception as well as a barrier method during treatment with efavirenz tablets and for 12 weeks after discontinuing efavirenz tablets. Advise patients to contact their healthcare provider if they plan to become pregnant, become pregnant, or if pregnancy is suspected during treatment with efavirenz tablets [*see Warnings and Precautions (5.7) and Use in Specific Populations (8.1, 8.3)*].

Pregnancy Exposure Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to efavirenz tablets during pregnancy *[see Use in Specific Populations (8.1)]*.

Fat Redistribution

Patients should be informed that 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 [*see Warnings and Precautions (5.13)*].

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By: HETERO™
Hetero Labs Limited
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next dose at your regularly scheduled time. If you need help in planning the best times to take your medicine, ask your doctor or pharmacist.

- If you take too much efavirenz tablets, call your doctor or go to the nearest hospital emergency room right away.
- When your efavirenz tablets supply starts to run low, get more from your doctor or pharmacy. It is important not to run out of efavirenz tablets. The amount of HIV-1 in your blood may increase if the medicine is stopped for even a short time. The virus may become resistant to efavirenz tablets and harder to treat.

What are the possible side effects of efavirenz tablets?

Efavirenz tablets may cause serious side effects, including:

- **Serious mental health problems** can happen in people who take efavirenz tablets. Tell your doctor right away if you have any of the following symptoms:
  - feel sad or hopeless
  - feel anxious or restless
  - have thoughts of hurting yourself (suicide) or have tried to hurt yourself or others
  - are not able to tell the difference between what is true or real and what is false or unreal
  - do not trust other people
  - hear or see things that are not real
  - are not able to move or speak normally.
- **Nervous system symptoms** are common in people who take efavirenz tablets and can be severe. These symptoms usually begin during the first or second day of treatment with efavirenz tablets and usually go away after 2 to 4 weeks of treatment. These symptoms may become worse if you drink alcohol, take a medicine for mental health problems, or use certain street drugs during treatment with efavirenz tablets. Symptoms may include:
  - dizziness
  - trouble concentration
  - drowsiness
  - trouble sleeping
  - unusual dreams

  If you have dizziness, trouble concentrating or drowsiness, do not drive a car, use machinery, or do anything that needs you to be alert.
- **Skin rash** is common with efavirenz tablets but can sometimes be severe. Skin rash usually goes away without any change in treatment. If you develop a rash with any of the following symptoms, tell your doctor right away:
  - skin rash, with or without itching
  - fever
  - swelling of your face
  - blisters or skin lesions
  - peeling skin
  - mouth sores
  - red or inflamed eyes, like "pink eye" (conjunctivitis)
- **Liver problems, including liver failure and death** can happen in people who take efavirenz tablets. Liver problems can also happen in people without a history of liver problems. Your doctor will do blood tests to check your liver before you start efavirenz and during treatment. Tell your doctor right away if you get any of the following symptoms:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - your urine turns dark
  - your bowel movements (stools) turn light in color
  - you don't feel like eating food for several days or longer
  - you feel sick to your stomach (nausea)
  - you have lower stomach area (abdominal) pain
- **Seizures** can happen in people who take efavirenz tablets. Seizures are more likely to happen if you have had seizures in the past. Tell your doctor if you have had a seizure or if you take a medicine to help prevent seizures.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor if you start having new symptoms after starting your HIV-1 medicine.
- **Changes in body fat** can happen in people who take HIV-1 medicine. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects of efavirenz tablets include:

- rash
- dizziness
- nausea
- headache
- difficulty concentrating
- abnormal dreams
- tiredness
- trouble sleeping
- vomiting

Some patients taking efavirenz tablets have experienced increased levels of lipids (cholesterol and triglycerides) in the blood. Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of efavirenz tablets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store efavirenz tablets?

- Store efavirenz tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep efavirenz tablets and all medicines out of the reach of children.

General information about efavirenz tablets

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use efavirenz tablets for a condition for which it was not prescribed. Do not give efavirenz tablets to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about efavirenz tablets that is written for health professionals.

For more information call 1-866-495-1995.

What are the ingredients in efavirenz tablets?

Active Ingredient: efavirenz, USP

Inactive ingredients:

Efavirenz tablets: microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate. The film coating contains Opadry® Yellow (hypromellose, titanium dioxide, iron oxide yellow and polyethylene glycol)

This Patient Information has been approved by the U.S. Food and Drug Administration.

Patient Information available at http://camberpharma.com/medication-guides

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