Between text matter to 2D Code the blank space should be min. 5mm.

Pharma code should be at least 8mm height after folding the Cutseals; this is minimum required height to read on line during packing.

Position / Orientation shall be changed depending upon the Printer's Machine suitability.

Do not print pink colour line.

- Space for 15 Digit Sequential 2D Data matrix Barcode shall be printed by the vendor.
- 2D data matrix should be minimum 8mm to 10mm height & width.
- 2D data matrix should be printed in the middle of the blank space in the folded Outset.

Efavirenz Tablets

1038524

Efavirenz Tablets

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**----------

Warnings and Precautions, Nervous System Symptoms (5.6)	10/2019
Warnings and Precautions, Immune Reconstitution Syndrome (5.12)	10/2019

----------**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 at least 3 months old and weighing at least3.5 kg. (1)

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

- Efavirenz tablets USP should be taken orally once daily on an empty stomach, preferably at bedtime. (2)
- Recommended adult dose: 600 mg. (2.2)
- With voriconazole, increase voriconazole maintenance dose to 400 mg every 12 hours and decrease efavirenz dose to 300 mg once daily using the capsule formulation. (2.2)
- With rifampin, increase Efavirenz dose to 800 mg once daily for patients weighing 50 kg or more. (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, usually begin 1-2 days after initiating therapy and resolve in 2-4 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 1-2 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 Strides Pharma Inc. at 1-877-244-9825 or go to www.strides.com 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 is 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: 02/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Efavirenz 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 *[see Warnings and Precautions (5.9)]*.

Efavirenz is 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 Populations (8.6)]*.

2.2 Adults

The recommended dosage of efavirenz is 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs). It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration of efavirenz 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 600 mg should be swallowed intact with liquid. For patients who cannot swallow tablets, the capsule sprinkle method of administration is recommended [*see Dosage and Administration (2.4)*]

Concomitant Antiretroviral Therapy

Efavirenz 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)*].

Dosage Adjustment

If efavirenz is coadministered with voriconazole, the voriconazole maintenance dose should be increased to 400 mg every 12 hours and the efavirenz dose should be decreased to 300 mg once daily using the capsule formulation (one 200 mg and two 50 mg capsules or six 50 mg capsules). Efavirenz tablets must not be broken. *[see Drug Interactions (7.1, Table 5)* and *Clinical Pharmacology (12.3, Tables 7 and 8)*].

If Efavirenz is coadministered with rifampin to patients weighing 50 kg or more, an increase in the dose of Efavirenz to 800 mg once daily is recommended *[see Drug Interactions (7.1, Table 5)* and *Clinical Pharmacology (12.3, Table 8)]*.

2.3 Pediatric Patients

It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime. Table 1 describes the recommended dose of efavirenz 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 for pediatric patients weighing 40 kg or greater is 600 mg once daily. For pediatric patients who cannot swallow capsules, the capsule contents can be administered with a small amount of food or infant formula using the capsule sprinkle method of administration [*see Dosage and Administration (2.4)*].

Table 1: Efavirenz Dosing in Pediatric Patients

Patient Body Weight	Efavirenz Daily Dose	Number of Capsules[a] or Tablets[b] and Strength to Administer
3.5 kg to less than 5 kg	100 mg	two 50 mg capsules
5 kg to less than 7.5 kg	150 mg	three 50 mg capsules
7.5 kg to less than 15 kg	200 mg	one 200 mg capsule
15 kg to less than 20 kg	250 mg	one 200 mg + one 50 mg capsule
20 kg to less than 25 kg	300 mg	one 200 mg + two 50 mg capsules
25 kg to less than 32.5 kg	350 mg	one 200 mg + three 50 mg capsules
32.5 kg to less than 40 kg	400 mg	two 200 mg capsules
at least 40 kg	600 mg	one 600 mg tablet OR three 200 mg capsules

[a]Capsules can be administered intact or as sprinkles [*see Dosage and Administration (2.4)*].
[b]Tablets must not be crushed.

2.4 Capsule Sprinkle Method of Administration:

For pediatric patients at least 3 months old and weighing at least 3.5 kg and adults who cannot swallow capsules or tablets, the capsule contents may be administered with a small amount (1 to 2 teaspoons) of food. Use of infant formula for mixing should only be considered for those young infants who cannot reliably consume solid foods. Patients and caregivers should be instructed to open the capsule carefully to avoid spillage or dispersion of the capsule contents into the air. The capsule should be held horizontally over a small container and carefully twisted to open. For patients able to tolerate solid foods, the entire capsule contents should be gently mixed with an age-appropriate soft food, such as applesauce, grape jelly, or yogurt, in the small container. For young infants receiving the capsule sprinkle-infant formula mixture, the entire capsule contents should be gently mixed into 2 teaspoons of reconstituted room temperature infant formula in a small container by carefully stirring with a small spoon, and then drawing up the mixture into a 10 mL oral dosing syringe for administration. After administration of the efavirenz-food or -formula mixture, an additional small amount (approximately 2 teaspoons) of food or formula must be added to the empty mixing container, stirred to disperse any remaining efavirenz residue, and administered to the patient. The efavirenz-food or -formula mixture should be administered within 30 minutes of mixing. No additional food should be consumed for 2 hours after administration of efavirenz.

3 DOSAGE FORMS AND STRENGTHS

- Tablets
  Efavirenz tablets, 600 mg are off white coloured, capsule shaped, film coated tablets imprinted with "EFZ" on one side and plain on other side.

4 CONTRAINDICATIONS

- Efavirenz is 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 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 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 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. In controlled trials of 1008 patients treated with regimens containing efavirenz for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among patients who received Efavirenz or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study 006, treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the Efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both Efavirenz-treated and control-treated patients. One percent of Efavirenz-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior although a causal relationship to the use of Efavirenz cannot be determined from these reports. 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, 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 (531/1008) of patients receiving Efavirenz in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens [*see Adverse Reactions (6.1, Table 3)*]. These symptoms included, but were not limited to, dizziness (28.1% of the 1008 patients), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in 2.0% of patients; and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing Efavirenz and from 3% to 5% in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms [*see Warnings and Precautions (5.5)*]. 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 + zidovudine + lamivudine, Efavirenz + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among Efavirenz-treated patients were generally similar to those in the indinavir-containing control arm.

Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Some events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms which are associated with increased efavirenz levels despite standard dosing of Efavirenz. Patients presenting with signs and symptoms of serious neurologic adverse experiences should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of Efavirenz is warranted.

Patients receiving Efavirenz should be alerted to the potential for additive central nervous system effects when Efavirenz is used concomitantly with alcohol or psychoactive drugs.

Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

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 to avoid pregnancy. [*See Use in Specific Populations (8.1 and 8.3)*.]

5.8 Rash

In controlled clinical trials, 26% (266/1008) of adult patients treated with 600 mg Efavirenz 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% (9/1008) of patients treated with Efavirenz. The incidence of Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in adult patients treated with Efavirenz in all studies and expanded access was 0.1%. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in adult clinical trials was 1.7% (17/1008).

Rash was reported in 59 of 182 pediatric patients (32%) treated with Efavirenz [*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 3-1642 days). Prophylaxis with appropriate antihistamines before initiating therapy with Efavirenz in pediatric patients should be considered.

Efavirenz can generally be reinitiated in patients interrupting therapy because of rash. Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. For patients who have had a life-threatening cutaneous reaction (eg, Stevens- Johnson syndrome), alternative therapy should be considered *[see Contraindications (4)]*.

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 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 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. 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 jirovecz* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) 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 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 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-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

Adverse Reactions	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI-, and Protease Inhibitor-Naive Patients		
	Efavirenz[a] + ZDV/LAM (n=412) 180 weeks[b]	Efavirenz[a] + Indinavir (n=415) 102 weeks[b]	Indinavir +ZDV/LAM (n=401) 76 weeks[b]	Efavirenz[a] + Nelfinavir + NRTIs (n=64) 71.1 weeks[b]	Efavirenz[a] + NRTIs (n=65) 70.9 weeks[b]	Nelfinavir +NRTIs (n=66) 62.7 weeks[b]
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[c]	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

[a] Includes adverse events at least possibly related to study drug or of unknown relationship for Study 006. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.
[b] Efavirenz provided as 600 mg once daily.
[c] Median duration of treatment.
[d] Includes erythema multiforme, rash, rash erythematous, rash follicular, rash maculopapular, rash petechial, rash pustular, and urticaria for Study 006 and macules, papules, rash, erythema, redness, inflammation, allergic rash, urticaria, welts, hives, itchy, and pruritus for ACTG 364.
— = Not Specified.
ZDV = zidovudine, LAM=lamivudine

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

Nervous System Symptoms

For 1008 patients treated with regimens containing Efavirenz 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 600 mg Once Daily (n=1008) %	Control Groups (n=635) %
Symptoms of any severity	52.7	24.6
Mild symptoms[c]	33.3	15.6
Moderate symptoms[d]	17.4	7.7
Severe symptoms[e]	2.0	1.3
Treatment discontinuation as a result of symptoms	2.1	1.1

[a] Includes events reported regardless of causality.
[b] Data from Study 006 and three Phase 2/3 studies.
[c] "Mild" = Symptoms which do not interfere with patient's daily activities.
[d] "Moderate" = Symptoms which may interfere with daily activities.
[e] "Severe" = Events which interrupt patient's usual daily activities.

Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with Efavirenz. In controlled trials, psychiatric symptoms observed at a frequency greater than 2% among patients treated with Efavirenz 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 1008 adults treated with regimens containing Efavirenz 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-treated patients and 0.3% for control groups, and the frequency of Grade 4 rash was 0.1% for Efavirenz and 0 for control groups. The discontinuation rates as a result of rash were 1.7% for Efavirenz-treated patients and 0.3% for control groups *[see Warnings and Precautions (5.8)]*.

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

Laboratory Abnormalities

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

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

Variable	Limit	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI-, and Protease Inhibitor-Naive Patients		
		Efavirenz[a] + ZDV/LAM (n=412) 180 weeks[b]	Efavirenz[a] + Indinavir (n=415) 102 weeks[b]	Indinavir + ZDV/LAM (n=401) 76 weeks[b]	Efavirenz[a] + Nelfinavir + NRTIs (n=64) 71.1 weeks[b]	Efavirenz[a] + NRTIs (n=65) 70.9 weeks[b]	Nelfinavir + NRTIs (n=66) 62.7 weeks[b]
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]	≥751 mg/dL	9%	6%	6%	11%	8%	17%
Hematology							
Neutrophils	<750/mm³	10%	3%	5%	2%	3%	2%

[a] Efavirenz provided as 600 mg once daily.
[b] Median duration of treatment.
[c] Isolated elevations of GGT in patients receiving Efavirenz may reflect enzyme induction not associated with liver toxicity.
[d] Nonfasting.
ZDV = zidovudine, LAM = lamivudine, ULN = Upper limit of normal, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyltransferase.

Patients Coinfected with Hepatitis B or C

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

Lipids

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

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 are summarized in Table 5. For pharmacokinetics data, [*see Clinical Pharmacology (12.3)*] Tables 7 and 8. This table 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

| Concom

doctor or pharmacy. It is important not to run out of Efavirenz. 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 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. 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 and can be severe. These symptoms usually begin during the first or second day of treatment with Efavirenz and usually go away after 2 to 4 weeks of treatment. Some symptoms may occur months to years after beginning Efavirenz therapy. 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. Symptoms may include:
  - dizziness
  - trouble concentrating
  - drowsiness
  - trouble sleeping
  - unusual dreams
  - lack of coordination or difficulty with balance

  If you have dizziness, trouble concentrating or drowsiness, do not drive a car, use machinery, or do anything that needs you to be alert. Some nervous system symptoms (e.g. confusion, slow thoughts and physical movement, and delusions [false beliefs] or hallucinations [seeing or hearing things that others do not see or hear]) may occur months to years after beginning Efavirenz therapy. Promptly contact your health care provider should any of these symptoms occur.
  - **Skin rash** is common with Efavirenz 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. Liver problems can 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. 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 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. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to Strides Pharma Inc. at 1-877-244-9825 or go to www.strides.com or FDA at 1-800- FDA-1088 or www.fda.gov medwatch

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 for a condition for which it was not prescribed. Do not give Efavirenz 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 that is written for health professionals. For more information, you can go to www.strides.com or call 1-877-244-9825.

What are the ingredients in Efavirenz tablets?

Active ingredient: efavirenz

Inactive ingredients:

Efavirenz tablets: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet film coating contains Instacoat Universal/Opacode black ink. Instacoat Universal contains HPMC 2910/ Hypromellose, titanium dioxide, polyethylene glycol, red iron oxide, black iron oxide and yellow iron oxide. Opacode black ink contains propylene glycol, shellac glaze and ferrosoferric oxide.

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

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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 breastfed.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Females of reproductive potential should undergo pregnancy testing before initiation of Efavirenz.

Contraception

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

8.4 Pediatric Use

The safety, pharmacokinetic profile, and virologic and immunologic responses of Efavirenz 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 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 have not been evaluated in this age group and there is a risk of developing HIV resistance if Efavirenz is underdosed. *See Dosage and Administration (2.2)* for dosing recommendations for pediatric patients.

8.5 Geriatric Use

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

8.6 Hepatic Impairment

Efavirenz is not recommended for patients with moderate or severe hepatic impairment because there are insufficient data to determine whether dose adjustment is necessary. Patients with mild hepatic impairment may be treated with efavirenz without any adjustment in dose. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering Efavirenz to these patients [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 should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with Efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

11 DESCRIPTION

Efavirenz tablet USP is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Efavirenz 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 is a white to off-white crystalline powder with a molecular mass of 315.68. It is practically insoluble in water (<10 microgram/mL).

Efavirenz tablet USP is available as capsule shaped film-coated tablets imprinted with "EFZ" on one side and plain on other side for oral administration containing 600 mg of efavirenz and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The film coating contains Instacoat Universal/Opacode black ink. Instacoat Universal contains HPMC 2910/Hypromellose, titanium dioxide, polyethylene glycol, red iron oxide, black iron oxide and yellow iron oxide. Opacode black ink contains propylene glycol, shellac glaze and ferrosoferric oxide.

FDA approved dissolution method differs from that of the USP.

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 C_{max} 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 C_{max} 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 1.6-9.1 μM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

In HIV-1-infected patients at steady state, mean C_{max}, mean 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 3-5 hours and steady-state plasma concentrations were reached in 6-10 days. In 35 patients receiving Efavirenz 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 1000 kcal, 500-600 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)*.]

Capsules: Administration of a single 600 mg dose of efavirenz capsules with a high-fat/high-caloric meal (894 kcal, 54 g fat, 54% calories from fat) or a reduced-fat/normal-caloric meal (440 kcal, 2 g fat, 4% calories from fat) was associated with a mean increase of 22% and 17% in efavirenz AUC∞ and a mean increase of 39% and 51% in efavirenz C_{max}, respectively, relative to the exposures achieved when given under fasted conditions. *[See Dosage and Administration (2) and Patient Counseling Information (17)]*

Bioavailability of capsule contents mixed with food vehicles:

In healthy adult subjects, the efavirenz AUC when administered as the contents of three 200 mg capsules mixed with 2 teaspoons of certain food vehicles (applesauce, grape jelly or yogurt, or infant formula) met bioequivalency criteria for the AUC of the intact capsule formulation administered under fasted conditions.

Distribution

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

Metabolism

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

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

Elimination

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

Special Populations

Pediatric: The pharmacokinetic parameters for efavirenz at steady state in pediatric patients were predicted by a population pharmacokinetic model and are summarized in Table 6 by weight ranges that correspond to the recommended doses.

Table 6: Predicted Steady-State Pharmacokinetics of Recommended Doses of Efavirenz (Capsules/Capsule Sprinkles) in HIV-Infected Pediatric Patients

Body weight	Dose	Mean $AUC_{0-24\ hr}$ μM.h	Mean C_{max} μg/mL	Mean C_{min} μg/mL
3.5-5 kg	100 mg	220.52	5.81	2.43
5-7.5 kg	150 mg	262.62	7.07	2.71
7.5-10 kg	200 mg	284.28	7.75	2.87
10-15 kg	200 mg	238.14	6.54	2.32
15-20 kg	250 mg	233.98	6.47	2.3
20-25 kg	300 mg	257.56	7.04	2.55
25-32.5 kg	350 mg	262.37	7.12	2.68
32.5-40 kg	400 mg	259.79	6.96	2.69
>40 kg	600 mg	254.78	6.57	2.82

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 isoymes 2C9 and 2C19 with K_i values (8.5-17 μM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82-160 μM) only at concentrations well above those achieved clinically. Coadministration of efavirenz with drugs primarily metabolized by 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/ritonavir 100 mg qd d 11-24 (pm) (simultaneous with efavirenz)	600 mg qd with a light snack d 11-24 (pm)	14	↑ 17% (8-27%)	↔	↓ 42% (31-51%)
Indinavir	1000 mg q8h x 10 days	600 mg qd x 10 days	20			
	After morning dose			↔[a]	↓ 33%[a] (26-39%)	↓ 39%[a] (24-51%)
	After afternoon dose			↔[a]	↓ 37%[a] (26-46%)	↓ 52%[a] (47-57%)
	After evening dose			↓ 29%[a] (11-43%)	↓ 46%[a] (37-54%)	↓ 57%[a] (50-63%)
Lopinavir/ Ritonavir	400/100 mg capsule 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 q12h 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 x 8 days	600 mg qd x 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]	1200 mg q8h x 10 days	600 mg qd x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%)[e]
Lamivudine	150 mg q12h x 14 days	600 mg qd x 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%[i]	↓ 77%[i]	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 (6 4-tablet doses over 3 days)	600 mg qd x 26 days	12			
Artemether				↓ 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% (28-57%)	↓ 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[i]
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-monodesmethyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol/ Norgestimate	0.035 mg/ 0.25 mg x 14 days	600 mg qd x 14 days				
Ethinyl estradiol			21	↔	↔	↔
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 35-100mg daily	600 mg qd x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Bupropion	150 mg single dose	600 mg qd x 13		↓ 34%	↓ 55%	NA
Hydroxy-bupropion	(sustained-release)	14 days		(21-47%)	(48-62%)	NA
				↑ 50% (20-80%)	↔	
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]	1200 mg q8h x 10 days	600 mg qd x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%)[b]
Tenofovir[d]	300 mg qd	600 mg qd x 14 days	30	↔	↔	↔
Boceprevir	800 mg tid x 6 days	600 mg qdx16days	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%[i] (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 × 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 90-95% (EC_{90-95}) ranged from 1.7 to 25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/monocyte cultures. Efavirenz demonstrated antiviral activity against clade B and most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses. Efavirenz demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine and nevirapine, NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. Efavirenz demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. Efavirenz was not antagonistic with adefovir, used for the treatment of hepatitis B virus infection, or ribavirin, used in combination with interferon for the treatment of hepatitis C virus infection.

Resistance

In cell culture

In cell culture, HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in EC_{50} 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 4-106 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 ph