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

5.10 Convulsions

5.12 Immune Reconstitution Syndrome

5.13 Fat Redistribution

Efavirenz can generally be reinitiated in patients interrupting therapy because of rash. Efavirenz should be discontinued in patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range.

5.5 Psychiatric Symptoms

There have been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior although a causal relationship to efavirenz is unclear. Studies of psychiatric symptoms in clinical trials showed a significantly increased frequency of depression and anxiety-like symptoms (7.4% for all dose levels of efavirenz versus 3.1% for placebo) during the first month of therapy. Severe neuropsychiatric symptoms such as delusions and psychosis-like phenomena may occur during treatment with efavirenz. If a psychiatric condition develops, or if a marked decrease in psychotic symptoms occurs, discontinuation of efavirenz should be considered. In a study of the frequency (regardless of causality) of specific serious psychiatric events among patients who received efavirenz or control regimens, compared with placebo, the estimated incidence of adverse reactions was 14.5% for efavirenz versus 11.3% for placebo.

5.6 Neurologic Symptoms

There have been isolated postmarketing reports of altered mental status, confusion, and changes in behavior, including death by suicide, while receiving efavirenz. The relationship of these events to efavirenz is unclear. There have been isolated reports of new-onset nervous system symptoms among efavirenz-treated patients. New-onset nervous system symptoms (regardless of causality) were reported in 1.9% of patients on efavirenz versus 0.6% of patients on placebo in a 66-week trial of efavirenz in combination with emtricitabine and tenofovir disoproxil fumarate. Most events of new-onset nervous system symptoms occurred within the first 12 weeks of treatment. The most common symptoms among patients undergoing new-onset nervous system symptoms were headache, dizziness, and depression (approximately one third of the total). New-onset nervous system symptoms were generally mild to moderate in severity and generally did not require discontinuation of efavirenz. Three of the 11 patients with new-onset nervous system symptoms discontinued efavirenz due to these events. (5.7)

5.7 Neuropsychologic Tests

Efavirenz can cause changes in the results of neuropsychologic tests. Serum levels of GGT, an enzyme involved in the metabolism of some antiretroviral agents, were increased in two phase 3 trials. GGT = gamma-glutamyltransferase.

5.8 Increased Serum Transaminases

Serum aminotransferase (ALT) and gamma-glutamyl transferase (GGT) levels have increased during efavirenz treatment. Serum transaminase elevations have generally been mild to moderate in severity and have resolved with interruption or discontinuation of therapy in most cases. Persistent elevations of serum transaminases can occur. In a 48-week trial, the incidence of transaminase elevations of at least two times the upper limit of normal (ULN) was 1.9% for efavirenz versus 1.1% for placebo. The most common elevations were ALT and GGT. Elevations of serum transaminases were more common in patients with detectable HIV RNA levels at baseline and in patients with impaired liver function. Elevated transaminases generally occurred during the first month of therapy. Patients with detectable HIV RNA levels at baseline and patients with impaired liver function should be monitored more closely during therapy with efavirenz. (5.9)

5.9 Inhibitors of CYP3A4

Efavirenz is a substrate of CYP3A4. Drugs that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, fluconazole, clarithromycin, azithromycin, cyclosporine, ritonavir, and nelfinavir) are not recommended because it may result in loss of therapeutic effect of efavirenz.

5.10 Efavirenz and Other Antiretroviral Drugs

Efavirenz tablets may be taken with or without food. Efavirenz tablets are not bioequivalent with Efavirenz Tablets PLR (Unscored). Efavirenz tablets must not be broken. Efavirenz and voriconazole should not be coadministered at standard doses. The coadministration of efavirenz and sofosbuvir/velpatasvir/voxilaprevir is not recommended because it may result in loss of therapeutic effect of efavirenz.

6 CLINICAL PHARMACOLOGY

Efavirenz is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Efavirenz is chemically described as (S)-6-chloro-3,4-dihydro-1,2-dimethyl-4-[(1-methyl-2-propenyl)amino]-1-naphthaleneacetamide. Efavirenz is a yellow, odorless, crystalline solid. Efavirenz is very soluble in dimethylformamide, soluble in methanol, slightly soluble in ethanol and acetic acid, and insoluble in water. Efavirenz crystallizes as white, rhombic needles. Efavirenz is a racemic mixture of (+)- and (-)-enantiomers. (5.11)

Clinical Pharmacology

Efavirenz is primarily metabolized by the cytochrome P450 (CYP) 3A4 pathway. Clinically significant decreases in efavirenz plasma concentrations are generally observed in patients receiving concomitant rifampin. Rifampin increases the clearance of efavirenz and may result in loss of therapeutic effect. (5.4) Coadministration of efavirenz and rifampin should be avoided. Efavirenz can generally be reinitiated in patients interrupting therapy because of rash. Efavirenz should be discontinued in patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range. Dehydration, renal disease, and hepatic disease may decrease the clearance of efavirenz. Patients with renal insufficiency should be monitored closely during treatment with efavirenz tablets.

8.2 Lactation

The effects of efavirenz on human milk have not been evaluated. The decision to breastfeed should be based on the importance of the drug to the mother and the potential risk to the infant. There are retrospective postmarketing reports of findings consistent with neural tube defects, including meningomyelocele, all in infants exposed to efavirenz during the first trimester. There are retrospective case reports of neural tube defects in infants whose mothers were exposed to efavirenz-containing regimens in later trimesters. There are no adequate, well-controlled studies in pregnant women. Inhibition of HIV-1 reverse transcriptase, which is present in the placenta, has been demonstrated. However, the risk of fetal harm cannot be ruled out. Use of efavirenz in pregnancy is not recommended unless no other appropriate therapy is available. (5.18)
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**Croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline**

**Hepatic impairment:**

- Impairment (Child-Pugh Class B or C) affects efavirenz pharmacokinetics.
- Administration of a single 600 mg efavirenz tablet with a high-fat/high-caloric meal (approximately 1000 kcal, 500 to 600 kcal) reduces efavirenz exposure by about 25%.

**Efficacy and Mechanism of Action:**

- Efavirenz has been shown to be effective in delaying the development of resistance to delavirdine and nevirapine, but not to amprenavir and indinavir.
- Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that inhibits the reverse transcriptase enzyme.
- Efavirenz also impairs CYP3A, CYP2C19, and CYP2B6, which can lead to increased levels of other coadministered medications.

**Pharmacokinetics:**

- Efavirenz has a mean steady-state plasma half-life of about 10 hours.
- Efavirenz is extensively metabolized by the liver and is excreted primarily in the urine.

**Elimination:**

- Efavirenz is eliminated with a terminal half-life of about 10 hours.
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**Contraindications:**

- Efavirenz is contraindicated in patients with a history of allergic reaction to efavirenz, indinavir, or any component of the formulation.
- Efavirenz is also contraindicated in patients with a history of a hypersensitivity reaction to efavirenz, indinavir, or any component of the formulation.

**Warnings:**

- Efavirenz is a CNS-active medication and can cause central nervous system (CNS) effects, including dizziness, drowsiness, and impaired judgment.
- Efavirenz is also a potential teratogen and can cause birth defects if taken during pregnancy.

**Precautions:**

- Efavirenz is a potential teratogen and can cause birth defects if taken during pregnancy.
- Efavirenz is a potential teratogen and can cause birth defects if taken during pregnancy.

**Adverse Reactions:**

- Nervous System Symptoms: Dizziness, drowsiness, impaired judgment, headache, fatigue, insomnia
- Skin Rashes: Erythema, rash, pruritus, urticaria, skin reactions
- Nausea, vomiting, diarrhea, anorexia, abdominal discomfort

**Drug Interactions:**

- Efavirenz can interact with other medications that are metabolized by the CYP3A enzyme system.
- Efavirenz can also cause QT prolongation and may be associated with torsades de pointes.

**Dosage and Administration:**

- Efavirenz tablets are a prescription HIV-1 medicine used with other antiretroviral medicines to treat HIV-1 infection in adults and pediatric patients.
- The recommended dose of efavirenz is 600 mg once daily.
- Efavirenz tablets are indicated for use in adults and pediatric patients weighing at least 15 kg.

**Overdosage:**

- Overdosage of efavirenz may result in symptoms of toxicity, including nausea, vomiting, diarrhea, abdominal discomfort, rash, dizziness, drowsiness, impaired judgment, headache, and fatigue.

**Patient Counseling:**

- Patients should be advised to report to their doctor the use of any other prescription or nonprescription medications they are taking.
- Patients should be advised to take efavirenz at the regularly scheduled time.
- Patients should be advised to watch for early warning signs of liver inflammation or failure, such as fatigue, anorexia, nausea, vomiting, diarrhea, and abdominal pain.
- Patients should be advised to inform their doctor if they develop a rash with any of the following symptoms: fever, swelling, pain, irritation, or changes in the rash.