HIGHLIGHTS OF PRESCRIBING INFORMATION **POM Schedule: S2 NS2 PP**

These highlights do not include all the information needed to use efavirenz, lamivudine and tenofovir disoproxil fumarate safely and effectively. See full prescribing information for efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

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

Cateogry of distribution: Prescription preparation

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

- **Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including lamivudine and tenofovir disoproxil fumarate. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)**
- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)**

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

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, a combination of one non-nucleoside reverse transcriptase inhibitor (efavirenz) and two nucleo(t)side reverse transcriptase inhibitors (lamivudine and tenofovir disoproxil fumarate), are indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 40 kg. (1)

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

- Recommended dose: One tablet (containing 600 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) taken once daily orally on an empty stomach, preferably at bedtime. (2.1)

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

Tablets: 600 mg efavirenz, 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate. (3)

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

- Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets are contraindicated in patients with previously demonstrated and clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4.1)
- For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). (4.2)

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

- Lactic acidosis and severe hepatomegaly with steatosis: Reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)
- Severe acute exacerbations of hepatitis B: Reported in patients who are co-infected with hepatitis B virus and HIV-1 and have discontinued lamivudine or tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
- Coadministration with Other Products: Do not use with other efavirenz, lamivudine or tenofovir containing products or emtricitabine-containing products. Do not administer in combination with adefovir dipivoxil. (5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue Efavirenz, Lamivudine and Tenofovir disoproxil fumarate as clinically appropriate. (5.5)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl with tenofovir disoproxil fumarate, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. Monitor CrCl and ser at risk. Avoid administering lamivudine and tenofovir disoproxil fumarate with concurrent or recent use of n
- Serious psychiatric symptoms: Immediate medical evaluation is recommended for serious psychiatric symptoms such as sev ideation./ 5.7, 17.1)
- Nervous system symptoms (NSS): NSS are frequent, usually begin 1 to 2 days after initiating therapy and resolve in 2 to 4 wee improve tolerability. NSS are not predictive of onset of psychiatric symptoms. (5.8, 17.1)
- Pregnancy: Fetal harm can occur when administered to a pregnant woman during the first trimester. Women should be appris the fetus. (5.9, 17.1) Pregnancy registry is available (8.1)
- Hepatotoxicity: Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including h marked transaminase elevations, or who are taking medications associated with liver toxicity. Among reported cases of hepati patients with no pre-existing hepatic disease. (5.11, 8.7)
- Rash: Rash usually begins within 1 to 2 weeks after initiating therapy and resolves within 4 weeks. Discontinue if severe ra
- Convulsions: Use caution in patients with a history of seizures. (5.12)
- Lipids: Total cholesterol and triglyceride elevations. Monitor before therapy and periodically thereafter. (5.13)
- Decreases in bone mineral density (BMD): Observed in HIV-infected patients. Consider assessment of BMD in patients with a his or other risk factors for osteoporosis or bone loss. (5.14)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.15)
- Redistribution/accumulation of body fat: Observed in HIV-infected patients receiving antiretroviral combination therapy. (5.16)

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

- Most common adverse reactions are headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, rash, dizziness, i asthenia, and cough. (6)

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

- Didanosine: Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine neuropathy) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted. (7. 3)
- Atazanavir: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with disoproxil fumarate only with ritonavir; monitor for evidence of tenofovir toxicity. (7. 4)
- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7. 5)

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

- Pregnancy: Women should avoid pregnancy during efavirenz therapy, a component of Efavirenz, Lamivudine and Tenofovir Di 12 weeks after discontinuation. (5.9)
- Nursing mothers: Women infected with HIV should be instructed not to breast-feed. (8.3)
- Hepatic impairment: Efavirenz is not recommended for patients with moderate or severe hepatic impairment. Use caution in impairment. (8.7)
- Pediatric patients: The incidence of rash was higher than in adults. (5.10, 6.1, 8.4)

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

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including lamivudine and tenofovir disoproxil fumarate. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *(See Warnings and Precautions (5.1))*.

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment *(See Warnings and Precautions (5.2))*.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

2.2 Dose Adjustment for Renal Impairment

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

3 DOSAGE FORMS AND STRENGTHS

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets, 600 mg/300 mg/300 mg are yellow colored, capsule shaped, bevel edged biconvex film coated tablets debossed with 'I' on one side and '127' on the other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate 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 contained in the formulation.

4.2 Contraindicated Drugs

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

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
HIV antiviral agents		
Posaconazole	↓ posaconazole*	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ clarithromycin* ↑ 14-OH metabolite*	Plasma concentrations decreased by efavirenz; clinical significance u volunteers, 46% developed rash while receiving efavirenz and clarithromy of efavirenz is recommended when given with clarithromycin. Alternative as azithromycin, should be considered (see *Other Drugs*, following table). Ot such as erythromycin, have not been studied in combina
Antimycobacterial: Rifabutin	↓ rifabutin*	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin rifabutin is given 2 or 3 times a week.
Rifampin	↓ efavirenz*	If efavirenz is coadministered with rifampin to patients weighing 50 kg or dose of efavirenz to 800 mg once daily is recommended.
Calcium channel blockers: Diltiazem	↓ diltiazem* ↓ desacetyl diltiazem* ↓ N-monodesmethyl diltiazem*	Diltiazem dose adjustments should be guided by clinical response (refer information for diltiazem). No dose adjustment of efavirenz is necessary diltiazem.
Others (eg, felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	No data are available on the potential interactions of efavirenz with other c that are substrates of CYP3A. The potential exists for reduction in plasm calcium channel blocker. Dose adjustments should be guided by clinical r prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin* ↓ pravastatin* ↓ simvastatin*	Plasma concentrations of atorvastatin, pravastatin, and simvastatin de prescribing information for the HMG-CoA reductase inhibitor for guidan dose.