PRODUCT MONOGRAPH

[Pr] Mylan-Efavirenz

(efavirenz tablets)

600 mg

Antiretroviral Agent

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(efavirenz tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets / 600 mg	Croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium lauryl sulphate and titanium dioxide.

INDICATIONS AND CLINICAL USE

Mylan-Efavirenz (efavirenz) is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

CONTRAINDICATIONS

Mylan-Efavirenz (efavirenz) is contraindicated in patients with clinically significant hypersensitivity to any of its components. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Mylan-Efavirenz must not be administered concurrently with cisapride[1], midazolam, triazolam, pimozide or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (e.g., cardiac arrhythmias, prolonged sedation or respiratory depression). (See **Table 1**.)

Coadministration of efavirenz with elbasvir and grazoprevir is contraindicated, due to the potential for significant decreases in plasma concentrations of elbasvir and grazoprevir. This effect is due to an induction of CYP3A4 by efavirenz, and may result in loss of therapeutic effect.
Herbal preparations containing St. John's wort (*Hypericum perforatum*) must not be used while taking Mylan-Efavirenz due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz.

[1] Cisapride is not marketed in Canada.

Table 1

Drugs That Are Contraindicated With Efavirenz		
Drug Class	**Drugs Within Class Contraindicated With Efavirenz**	**Clinical Comment**
Benzodiazepines	midazolam, triazolam	Potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
GI Motility Agents	Cisapride*	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Anti-Migraine	ergot derivatives (dihydroergotamine, ergonovine, ergotamine)	Potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Neuroleptic	pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Hepatitis C antiviral agents	Elbasvir/grazoprevir	May lead to loss of therapeutic effect of elbasvir/grazoprevir.
Herbal Products	St. John's wort (*Hypericum perforatum*)	May lead to loss of virologic response and possible resistance to efavirenz or to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

*not marketed in Canada

WARNINGS AND PRECAUTIONS

General

Coadministration of efavirenz with ATRIPLA, a fixed-dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate, is not recommended, unless needed for dose adjustment (e.g, with rifampin).

Effects on Ability to Drive and To Use Machines:

Efavirenz may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that, if they experience these symptoms, they should avoid potentially hazardous tasks such as driving or operating machinery (see **Neurologic**).

Carcinogenesis, Mutagenesis and Impairment of Fertility (see **Part II: TOXICOLOGY**)

Cardiovascular

QTc prolongation has been observed with the use of efavirenz (see **DRUG INTERACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**). 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.

Endocrine and Metabolism

Serum Lipids and Blood Glucose:
Serum lipid and blood glucose levels may increase during antiretroviral therapy (ART). Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

Hepatic/Biliary/Pancreatic

Postmarketing reports of hepatic failure have occurred including some cases in patients without pre-existing hepatic disease or other identifiable risk factors (see **Monitoring and Laboratory Tests; Liver Enzymes**).

In controlled clinical studies the rate of clinical pancreatitis was similar in patients receiving 1/1008 (0.1%) and not receiving efavirenz 2/635 (0.3%).

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 **ADVERSE REACTIONS; Abnormal Hematologic and Clinical Chemistry Findings**).

Elevated triglycerides have been reported in patients receiving efavirenz, in some cases to levels which can predispose a patient to pancreatitis. Among patients with elevated triglycerides, there have been no cases of pancreatitis. Because these triglyceride levels were not obtained in a fasting state, the exact clinical relevance of these measurements is not known.

Hypersensitivity Reactions

In clinical trials, hypersensitivity reactions were uncommon (<1%) in patients treated with efavirenz.

Immune

Immune Reconstitution Inflammatory Syndrome has been reported in patients treated with combination antiretroviral therapy, including efavirenz. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jijovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre 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.

Neurologic

Nervous System Symptoms:

Fifty-three percent of patients receiving efavirenz in controlled clinical trials reported central nervous system symptoms compared to 25% of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). In controlled trials, these symptoms were severe in 2.0% of patients receiving efavirenz 600 mg daily and in 1.3% of patients receiving control regimens. In clinical trials, 2.1% of efavirenz - treated patients discontinued therapy because of nervous system symptoms. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks. After 4 weeks of therapy the prevalence of nervous system symptoms of at least moderate severity ranged from 5-9% in patients treated with regimens containing efavirenz and from 3-5% in patients treated with a control regimen. Patients should be informed that these common nervous system symptoms are likely to improve with continued therapy. Dosing at bedtime improves tolerability of these symptoms (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Analysis of long-term data from Study AI266-006 (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.

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.

Seizures:

Caution should be taken in any patient with a history of seizures. Convulsions have been observed infrequently in patients receiving efavirenz, generally in the presence of known medical history of seizures. Overall, the rate of seizure in controlled clinical trials has been 0.89% in efavirenz treated patients and 0.63% in the control patients. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver such as phenytoin, carbamazepine, and phenobarbital, may require periodic monitoring of plasma levels (see **DRUG INTERACTIONS**).

Psychiatric:

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1008 patients treated with regimens containing efavirenz for an average of 2.1 years and 635 patients treated with control regimens for an average of 1.5 years, the frequency 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%), non-fatal 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 AI266-006, 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 AI266-006, 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 post marketing reports of death by suicide, delusions, and psychosis – like behavior and catatonia, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the probability 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**).

Sensitivity/Resistance:

Mylan-Efavirenz (efavirenz) must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, 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. (Please refer to the most recent antiretroviral guidelines for further information.)

Resistance:

Clinical isolates with reduced susceptibility in cell culture to efavirenz have been obtained. The most frequently observed amino acid substitution in clinical studies with efavirenz is K103N (54%). One or more RT substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188,
190, 225, 227, and 230 were observed in patients failing treatment with efavirenz in combination with other antiretrovirals. Other resistance mutations observed to emerge commonly included L100I (7%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%) (see **VIROLOGY**).

Cross-Resistance:

Cross-resistance has been recognized among NNRTIs. Clinical isolates previously characterized as efavirenz-resistant were also phenotypically resistant in cell culture to delavirdine and nevirapine compared to baseline. Delavirdine- and/or nevirapine-resistant clinical viral isolates with NNRTI resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A, Y181X, Y188X, G190X, P225H, F227L, or M230L) showed reduced susceptibility to efavirenz in cell culture (see **VIROLOGY**).

Skin:

Mylan-Efavirenz is not recommended for patients who have had a life-threatening cutaneous reaction (eg, Stevens-Johnson syndrome). Mylan-Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever.

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz experienced new onset skin rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation or ulceration occurred in 0.9% (9/1008) of patients treated with efavirenz. The median time to onset of rash in adults was 11 days and the median duration, 16 days. The discontinuation rate for rash in clinical trials was 6.4% (17/266) among patients with rash and 1.7% (17/1008) overall.

In clinical trials, grade 4 rash (including Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis and exfoliative dermatitis) was uncommon (<1%) in patients treated with efavirenz.

Rash was reported in 26 of 57 pediatric patients (46%) treated with efavirenz capsules. One pediatric patient experienced Grade 3 rash (confluent rash with fever), and two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in children was eight days. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered (see **ADVERSE REACTIONS**).

Special Populations

Pregnant Women:

Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving Mylan-Efavirenz and for 12 weeks after discontinuation. Barrier contraception must always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives) (see **DRUG INTERACTIONS** and **TOXICOLGY**). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of Mylan-Efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing prior to initiation of Mylan-Efavirenz (see Reproductive Risk Potential).

There are no adequate and well-controlled studies in pregnant women. Mylan-Efavirenz should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options.

Antiretroviral Pregnancy Registry
To monitor fetal outcomes of pregnant women exposed to efavirenz, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients,

http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

As of July 2013, the Antiretroviral Pregnancy Registry has received prospective reports of 1067 pregnancies exposed to efavirenz-containing regimens, 904 of which were first-trimester exposures. Birth defects occurred in 18 of 766 live births (first-trimester exposure) and 3 of 160 live births (second-/third-trimester exposure). One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first trimester exposure to efavirenz has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia.

There have been seven reports during post-marketing use of findings consistent with neural tube defects, including meningomyelocele, all in mothers exposed to efavirenz containing regimens (excluding any efavirenz-containing fixed-dose combination tablets) in the first trimester. Although a causal relationship of these events to the use of efavirenz cannot be established, similar defects have been observed in nonclinical studies of efavirenz (see **TOXICOLOGY, Reproduction and Teratology**).

Nursing Women:

It is currently recommended that HIV-infected women should not breast-feed to avoid postnatal transmission of HIV. Studies in rats have demonstrated that efavirenz is excreted in milk. **Mothers should be instructed not to breast-feed if they are receiving Mylan-Efavirenz**.

Pediatrics:

ACTG 382 is an ongoing open-label uncontrolled 48-week study in 57 NRTI-experienced pediatric patients to characterize the safety, pharmacokinetics, and antiviral activity of efavirenz in combination with nelfinavir (20-30 mg/kg TID) and NRTIs. Mean age was 8 years (range 3-16). Efavirenz has not been studied in pediatric patients below 3 years of age or who weigh less than 13 kg. At 48 weeks, the type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of rash which was reported in 46% (26/57) of pediatric patients compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric patients compared to 0.9% of adults (see **ADVERSE REACTIONS**).

The starting dose of efavirenz was 600 mg daily adjusted to body size, based on weight, targeting AUC levels in the range of 190-380 μM.h. The pharmacokinetics of efavirenz in pediatric

patients were similar to adults. In 48 pediatric patients receiving the equivalent of a 600 mg dose of efavirenz, steady-state C_{max} was 14.2 ± 5.8 μM (mean ± SD), steady-state C_{min} was 5.6 ± 4.1 μM, and AUC was 218 ± 104 μM.h (see also **DETAILED PHARMACOLOGY**).

Geriatrics:

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

Hepatic Impairment:

The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment and its use is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) because of insufficient data. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with mild hepatic impairment, caution should be exercised in administering Mylan-Efavirenz to these patients (see **Monitoring and Laboratory Tests; Liver Enzymes**, **ADVERSE REACTIONS**; **Abnormal Hematologic and Clinical Chemistry Findings**, **DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY**; Pharmacokinetics; Special Populations).

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; consequently, the impact of renal impairment on efavirenz elimination should be minimal. There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population (see **DOSAGE AND ADMINISTRATION**).

Monitoring and Laboratory Tests

Lipids:

Monitoring of cholesterol and triglycerides should be considered in patients treated with efavirenz (See **ADVERSE REACTIONS**; Abnormal Hematologic and Clinical Chemistry Findings).

Liver Enzymes:

In patients with underlying liver disease including Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. Postmarketing reports of hepatic failure have occurred including some cases in patients with no pre-existing hepatic disease or other identifiable risk factors (see **Post-Market Adverse Drug Reactions**). Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. In patients with persistent

elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the potential risks of significant liver toxicity (see **ADVERSE REACTIONS**; **Abnormal Hematologic and Clinical Chemistry Findings**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Efavirenz has been studied in 9200 patients. The most significant adverse events observed in patients treated with efavirenz are nervous system symptoms, psychiatric symptoms, and rash.

The long-term safety profile of efavirenz-containing regimens was evaluated in a controlled trial, in which patients received efavirenz + zidovudine + lamivudine (n = 412, median duration 180 weeks), efavirenz + indinavir (n = 415, median duration 102 weeks), or indinavir + zidovudine + lamivudine (n = 401, median duration 76 weeks). Long-term use of efavirenz in this study was not associated with any new safety concerns.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Nervous System Symptoms

Fifty-three percent of patients receiving efavirenz reported central nervous system symptoms (see **WARNINGS AND PRECAUTIONS**; Neurologic). Table 2 lists the frequency of the symptoms of different degrees of severity, and gives the discontinuation rates in clinical trials 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. The frequencies of specific central and peripheral nervous system symptoms are provided in Table 2.

Table 2
Percent of Patients with One or More Selected Nervous System Symptoms[1,2]

Percent of Patients with:	Efavirenz 600 mg daily (N=1008)	Control Groups (N= 635)
	%	%
Mild Symptoms[3]	33.3	15.6
Moderate Symptoms[4]	17.4	7.7
Severe Symptoms[5]	2	1.3
Symptoms of Any Severity	52.7	24.6
Treatment discontinuation as a result of symptoms	2.1	1.1

[1] Includes events reported regardless of causality.
[2] Data from Studies 006, 020 and two Phase II studies.
[3] "Mild" = Symptoms which do not interfere with patient's daily activities.
[4] "Moderate" = Symptoms which may interfere with daily activities.
[5] "Severe" = Symptoms which interrupt patient's usual daily activities.

Analysis of long-term data (median treatment duration 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 control arm.

Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials the frequency of specific serious psychiatric symptoms among patients who received efavirenz or control regimens, respectively, were: severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), non-fatal suicide attempts (0.5%, 0%), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%) and manic reactions (0.2%, 0.3%) (see **WARNINGS AND PRECAUTIONS**; Psychiatric). Additional psychiatric symptoms observed at a frequency of >2% among patients treated with efavirenz or control regimens respectively, in controlled clinical trials were depression (19%, 16%), anxiety (13%, 9%) and nervousness (7%, 2%).

Skin Rash

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with efavirenz. In most patients rash resolves with continuing efavirenz therapy within one month. Efavirenz can be reinitiated in patients interrupting therapy because of Grades 1 and 2 rash. Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. The frequency of rash by NCI grade and the discontinuation rates as a result of rash are provided in Table 3.

Table 3
Percent of Patients with Treatment-Emergent Rash[1,2]

Percent of Patients with:	Description of Rash Grade3	Efavirenz 600 mg once daily Adults (N= 1008) %	Efavirenz Pediatric Patients (N=57) %	Control Groups Adults (N= 635) %
Grade 1 Rash	Erythema, pruritus	10.7	8.8	9.8
Grade 2 Rash	Diffuse maculopapular rash, dry desquamation	14.7	31.6	7.4
Grade 3 Rash	Vesiculation, moist desquamation, ulceration	0.8	1.8	0.3

Percent of Patients with:	Description of Rash Grade3	Efavirenz 600 mg once daily Adults (N= 1008) %	Efavirenz Pediatric Patients (N=57) %	Control Groups Adults (N= 635) %
Grade 4 Rash	Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	0.1	3.5	0
Rash of Any Grade	—	26.3	45.6	17.5
Treatment discontinuation as a result of rash	—	1.7	8.8	0.3

[1] Includes events reported regardless of causality.
[2] Data from Studies 006, 020, and two Phase II studies.
[3] NCI (National Cancer Institute) Grading System.

As seen in Table 3, rash is more common in children and more often of higher grade (i.e., more severe) (see **WARNINGS AND PRECAUTIONS**; Skin).

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.

Selected clinical adverse experiences of moderate or severe intensity observed in ≥2% of efavirenz-treated patients in three controlled clinical trials are presented in Table 4.

Table 4
Selected Treatment-Emergent[1] Adverse Events of
Moderate or Severe Intensity Reported in ≥2% of Efavirenz-Treated Patients
in Studies DMP 266-006, ACTG 364 and DMP 266-020

Adverse Events	Study DMP 266-006 3TC, NNRTI and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced NNRTI and Protease Inhibitor-Naive Patients			Study DMP 266-020 NRTI-experienced NNRTI and Protease Inhibitor-Naive Patients	
	Efavirenz[2] + ZDV/3TC (N = 412) 180 weeks[3]	Efavirenz[2] + Indinavir (N =415) 102 weeks[3]	Indinavir + ZDV/3TC (N = 401) 76 weeks[3]	Efavirenz[2] + Nelfinavir + NRTIs (N = 64)	Efavirenz[2] + NRTIs (N = 65)	Nelfinavir + NRTIs (N = 66)	Efavirenz[2] + Indinavir + NRTIs (N = 154)	Indinavir + NRTIs (N = 168)
	%	%	%	%	%	%	%	%
Body as a Whole								
Fatigue	8	5	9	0	2	3	5	1
Pain	1	2	8	13	6	17	4	3
Central and Peripheral								

Adverse Events	Study DMP 266-006 3TC, NNRTI and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced NNRTI and Protease Inhibitor-Naive Patients			Study DMP 266-020 NRTI-experienced NNRTI and Protease Inhibitor-Naive Patients	
	Efavirenz[2] + ZDV/3TC (N = 412) 180 weeks[3]	Efavirenz[2] + Indinavir (N =415) 102 weeks[3]	Indinavir + ZDV/3TC (N = 401) 76 weeks[3]	Efavirenz[2] + Nelfinavir + NRTIs (N = 64)	Efavirenz[2] + NRTIs (N = 65)	Nelfinavir + NRTIs (N = 66)	Efavirenz[2] + Indinavir + NRTIs (N = 154)	Indinavir + NRTIs (N = 168)
	%	%	%	%	%	%	%	%
Nervous System								
Dizziness	9	9	2	2	6	6	7	1
Headache	8	5	3	5	2	3	5	4
Gastrointestinal								
Nausea	10	6	24	3	2	2	10	10
Vomiting	6	3	14	-	-	-	6	5
Diarrhea	3	5	6	14	3	9	11	3
Dyspepsia	4	4	6	0	0	2	3	1
Abdominal Pain	2	2	5	3	3	3	3	1
Psychiatric								
Concentration Impaired	5	3	<1	0	0	0	3	1
Insomnia	7	7	2	0	0	2	3	1
Anxiety	2	4	<1	-	-	-	2	1
Abnormal Dreams	3	1	0	-	-	-	2	1
Somnolence	2	2	<1	0	0	0	2	2
Depression	5	4	<1	3	0	5	2	0
Anorexia	1	<1	<1	0	2	2	5	1
Nervousness	2	2	0	2	0	2	1	0
Skin & Appendages								
Rash	11	16	5	9	5	9	10	6
Pruritus	<1	1	1	9	5	9	2	1

[1] Includes those adverse events at least possibly related to study drug or of unknown relationship for Studies 006 and 020. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.
[2] Efavirenz provided as 600 mg once daily.
[3] Median duration of treatment
- Not Specified
ZDV = zidovudine, 3TC = lamivudine

Lipodystrophy (any severity, regardless of relationship to study regimen) was reported in 3%, 4%, and 5% of patients treated with efavirenz + zidovudine + lamivudine, efavirenz + indinavir, and indinavir + zidovudine + lamivudine, respectively. The frequencies of other adverse event terms that may be associated with lipodystrophy (abdomen enlarged, breast enlargement, cachexia, gynecomastia, lipidosis, lipoma, and obesity) ranged from <1% to 3% and were similar among the treatment groups.

Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3 to 16 years who received efavirenz capsules, nelfinavir, and one or more NRTIs were: rash (46%), diarrhea/loose stools (39%), fever (21%), cough (16%), dizziness/lightheaded/fainting (16%), ache/pain/discomfort (14%), nausea/vomiting (12%), and headache (11%). The incidence of nervous system symptoms was 18% (10/57). One patient experienced Grade 3 rash, two patients had Grade 4 rash, and five patients (9%) discontinued because of rash (see **WARNINGS AND PRECAUTIONS**; Special Populations, Pediatrics).

Adverse clinical experiences of moderate to severe intensity observed in less than 2% of patients receiving efavirenz in all Phase II/III studies, including the North American expanded access program as well as post-marketing spontaneous reports, and considered at least possibly related or of unknown relationship to treatment are listed below by body system:

Body as a Whole: alcohol intolerance, allergic reaction, asthenia, fever, hot flushes, influenza-like symptoms, malaise, pain, peripheral edema, syncope, dysregulated body temperature, flank pain, hypersensitivity reaction. Redistribution/accumulation of body fat (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**).

Cardiovascular: arrhythmia, flushing, palpitations, tachycardia, thrombophlebitis, hypertension, congestive heart failure, chest pain

Central and Peripheral Nervous System: ataxia, confusion, convulsions, impaired coordination, migraine headaches, neuralgia, paresthesia, hypoesthesia, peripheral neuropathy, speech disorder, stupor, tremor, neuromuscular paresis, paranoid reaction

Gastrointestinal: dry mouth, pancreatitis, constipation, malabsorption

Liver and Biliary System: hepatic enzymes increased (including ALT, AST and GGT), hepatitis, jaundice, hepatomegaly (see **Post-Market Adverse Drug Reactions**)

Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia

Miscellaneous: thrombocytopenia, proteinuria, anemia, pancytopenia, increased sweating

Musculoskeletal: arthralgia, myalgia, myopathy, involuntary muscle contraction, muscle weakness, polyarthritis

Psychiatric: aggressive reactions, abnormal thinking, aggravated depression, agitation, delusions, amnesia, anxiety, apathy, delirium, depersonalization, emotional lability, euphoria, hallucination, manic reaction, psychosis, neurosis, paranoia, suicide, catatonia
Respiratory: asthma, apnea, dyspnea

Skin and Appendages: acne, alopecia, eczema, folliculitis, skin exfoliation, urticaria, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, verruca, nail disorders, skin disorders, photosensitivity reaction

Special Senses: abnormal vision, diplopia, glaucoma, iritis, parosmia, taste perversion, tinnitus

Urinary System: polyuria

Abnormal Hematologic and Clinical Chemistry Findings

Table 5 summarizes clinically important laboratory abnormalities reported in Study 006 and ACTG 364.

Table 5
Selected Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Efavirenz-Treated Patients in Studies 006 and ACTG 364

		Study 006 3TC-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI- and Protease Inhibitor-Naive Patients		
Variable	Limit	Efavirenz[a] + ZDV/3TC (n=412) 180 weeks[b]	Efavirenz[a] + Indinavir (n=415) 102 weeks[b]	Indinavir + ZDV/3TC (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, 3TC = lamivudine, ULN = Upper limit of normal, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyltransferase.

Liver Enzymes: Liver function should be monitored in patients with a prior history of Hepatitis B and/or C (see **WARNINGS AND PRECAUTIONS**; **Monitoring and Laboratory Tests**).

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 co-infected 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 co-infected 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.
Lipids: Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving efavirenz. In patients treated with efavirenz + ZDV + 3TC, increases in

non-fasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with efavirenz + IDV, increases in non-fasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed. Nonfasting total cholesterol levels ≥6.2 mmol/L and ≥7.8 mmol/L were reported in 34% and 9%, respectively, of patients treated with efavirenz + ZDV + 3TC; 54% and 20%, respectively, of patients treated with efavirenz + indinavir; and 28% and 4%, respectively, of patients treated with indinavir + ZDV + 3TC. The effects of efavirenz on triglycerides and LDL were not well-characterized since samples were taken from non-fasting patients. The clinical significance of these findings is unknown (see **WARNINGS AND PRECAUTIONS**; **Monitoring and Laboratory Tests**).

Serum Amylase: Asymptomatic elevations in serum amylase greater than 1.5 times the upper limit of normal were seen in 10% of patients treated with efavirenz and in 6% of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown (see **WARNINGS AND PRECAUTIONS**; **Hepatic/Biliary/Pancreatic**).

Post-Market Adverse Drug Reactions

Additional undesirable effects reported in postmarketing surveillance include neurosis, gynecomastia, rhabdomyolysis, increased CPK, blurred vision, photoallergic dermatitis, immune reconstitution inflammatory syndrome, cerebellar coordination and balance disturbances and vertigo.

Hepatic failure has been reported postmarketing, including some cases in patients with no pre-existing hepatic disease or other identifiable risk factors and also some cases characterized by a fulminant course, sometimes progressing to transplantation or death.

Additional cases of pancreatitis have been reported in postmarketing surveillance. Please see **WARNINGS AND PRECAUTIONS**: **Hepatic/Biliary/Pancreatic**.

DRUG INTERACTIONS

Overview

Efavirenz has been shown *in vivo* to induce CYP3A4 and CYP2B6. Other compounds that are substrates of CYP3A4 or CYP2B6 may have decreased plasma concentrations when coadministered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drug-Drug Interactions

Drugs which induce CYP3A4 activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with efavirenz are summarized in Tables 1, 6 and 7. (See also **PHARMACOKINETICS**; **Drug-Drug Interactions** and **CONTRAINDICATIONS.**)

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 **ACTION AND CLINICAL PHARMACOLOGY**). Consider alternatives to efavirenz when coadministered with a drug with a known risk of Torsade de Pointes.

The drugs listed in these tables are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 6

Established Drug Interactions		
Concomitant Drug Class: Drug Name	**Effect on Concentration**	**Clinical Comment**
Antiretroviral agents		
Protease inhibitor: Atazanavir	↓ atazanavir [a]	Efavirenz decreases atazanavir exposure (see Table 9, ACTION AND CLINICAL PHARMACOLOGY, Drug-Drug Interactions,). **For treatment-naive patients:** If atazanavir is combined with efavirenz, atazanavir 400 mg with ritonavir 100 mg should be administered once daily all as a single dose with food, and efavirenz should be administered on an empty stomach, preferably at bedtime. **For treatment-experienced patients:** Do not coadminister atazanavir with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir	For coadministration with fosamprenavir and ritonavir, the complete prescribing information for fosamprenavir calcium should be consulted.
Protease inhibitor: Indinavir	↓ indinavir [a]	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz. When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily), the indinavir AUC and $_{Cmin}$ were decreased on average by 33%-46% and 39-57%, respectively, compared to when indinavir (800 mg every 8 hours) was given alone.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir [a]	For lopinavir/ritonavir capsules or oral solution, a dose increase to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food is recommended when used in combination with efavirenz in patients for whom reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). **Lopinavir/ritonavir tablets should not be administered once- daily in combination with efavirenz.** In antiretroviral-naive patients, lopinavir/ritonavir tablets can be used twice daily in combination with efavirenz with no dose adjustment. A dose increase of lopinavir/ritonavir tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence).

Established Drug Interactions		
Concomitant Drug Class: Drug Name	**Effect on Concentration**	**Clinical Comment**
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc [a]	Refer to the full prescribing information for maraviroc for guidance on coadministration with efavirenz.
Integrase strand transfer inhibitor: Raltegravir	↓ raltegravir [a]	Efavirenz did not have a clinically meaningful effect on the pharmacokinetics of raltegravir.
Protease inhibitor: Ritonavir	↑ ritonavir [a] ↑efavirenz [a]	When ritonavir 500 mg q12h was coadministered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir [a]	Should not be used as sole protease inhibitor in combination with efavirenz.
Hepatitis C antiviral agents		
NS5B polymerase inhibitor /NS5A inhibitor: Sofosbuvir/ velpatasvir	↔ sofosbuvir ↓ velpatasvir ↔ efavirenz	Coadministration of sofosbuvir/velpatasvir with efavirenz is not recommended. Concomitant administration of sofosbuvir/velpatasvir with efavirenz resulted in a reduction (approximately 50%) in the systemic exposure of velpatasvir. The mechanism of the effect on velpatasvir is induction of CYP3A and CYP2B6 by efavirenz. Refer to the prescribing information for sofosbuvir/velpatasvir for more information.
Velpatasvir/ sofosbuvir/ voxilaprevir	↓velpatasvir ↓voxilaprevir	Concomitant administration of velpatasvir/sofosbuvir/ voxilaprevir with efavirenz is not recommended, as it may decrease concentrations of velpatasvir and voxilaprevir. Refer to the prescribing information for velpatasvir/ sofosbuvir/ voxilaprevir for more information.
Elbasvir/ grazoprevir	↓elbasvir ↓grazoprevir ↔efavirenz	Concomitant administration of efavirenz with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by CYP3A4 induction. Refer to the prescribing information for elbasvir/grazoprevir for more information.
Protease inhibitor: Glecaprevir/ pibrentasvir	↓glecaprevir ↓pibrentasvir ↔efavirenz	Concomitant administration of glecaprevir/pibrentasvir with efavirenz may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Coadministration of glecaprevir/pibrentasvir with Mylan-Efavirenz is not recommended. Refer to the prescribing information for glecaprevir/pibrentasvir for more information.
Other agents		
Anticonvulsants: Carbamazepine	↓ carbamazepine [a] ↓ efavirenz [a]	Plasma concentrations of carbamazepine and efavirenz decreased. Periodic monitoring of carbamazepine plasma levels should be conducted. There are insufficient data to make a dose recommendation. Alternative anticonvulsant treatment should be considered.

Established Drug Interactions		
Concomitant Drug Class: Drug Name	**Effect on Concentration**	**Clinical Comment**
Antidepressant: Bupropion	↓ bupropion [a]	The effect of efavirenz on bupropion exposure is thought to be due to the induction of bupropion metabolism. Bupropion dose adjustments should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz.
Sertraline	↓ sertraline [a]	Since efavirenz reduces sertraline levels, it may be necessary to retitrate the sertraline dose in order to achieve the desired clinical effect. In a drug interaction study in healthy subjects, an increased incidence of impaired concentration was seen in subjects receiving sertraline concomitantly with efavirenz.
Antifungal: Itraconazole	↓itraconazole [a] ↓ hydroxyitraconazole [a]	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Antifungal: Posaconazole	↓ posaconazole [a]	Avoid concomitant use of posaconazole and efavirenz unless the benefit to the patient outweighs the risk.
Antifungal: Voriconazole	↓ voriconazole [a] ↑efavirenz [a]	Standard doses of voriconazole and efavirenz should not be used concurrently. When voriconazole is coadministered with efavirenz, the voriconazole maintenance dose should be increased to 400 mg every 12 hours and efavirenz dose should be decreased to 300 mg once daily using the capsule formulation. Efavirenz tablets should not be broken.
Anti-infective: Clarithromycin	↓clarithromycin [a] ↑14-OH metabolite [a]	Consider alternatives to macrolide antibiotics because of the risk of QT interval prolongation. Plasma concentrations decreased by efavirenz; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered (see section on "Other Drugs", below Table 7). Not all macrolide antibiotics have been studied in combination with efavirenz.
Antimalarial: Artemether/ lumefantrine[b]:	↓ artemether [a] ↓ dihydroartemisinin [a] ↓ lumefantrine [a]	Consider alternatives to artemether/lumefantrine because of the risk of QT interval prolongation. Coadministration of efavirenz with artemether /lumefantrine resulted in a decrease in exposures to artemether, dihydroartemisinin (active metabolite of artemether), and lumefantrine. Exposure to efavirenz was not significantly affected. Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when efavirenz and artemether/lumefantrine tablets are coadministered.
Antimalarial: Atovaquone Proguanil	↓ atovaquone ↓ proguanil	Coadministration of efavirenz with atovaquone/ proguanil resulted in a decrease in exposures to atovaquone and proguanil. Since decreased concentrations of atovaquone and proguanil may result in a decrease of antimalarial efficacy, concomitant administration should be avoided whenever possible.
Antimycobacterial: Rifabutin	↓ rifabutin [a]	Consider an increase of the daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.

Established Drug Interactions		
Concomitant Drug Class: Drug Name	**Effect on Concentration**	**Clinical Comment**
Antimycobacterial: Rifampin	↓efavirenz [a]	Rifampin has the potential to decrease serum concentration of efavirenz. When efavirenz is coadministered with rifampin to adult patients weighing 50 kg or more, a dose increase of efavirenz to 800 mg once daily is recommended.
Calcium channel blocker: Diltiazem	↓diltiazema [a] ↓ desacetyl diltiazem [a] ↓N-monodesmethyl diltiazem [a]	Diltiazem levels are markedly decreased when coadministered with efavirenz. Efavirenz levels increased to a lesser extent (see Tables 9 and 10). Patients should be closely monitored for possible decreased diltiazem effects and increased adverse events and laboratory abnormalities associated with efavirenz. Refer to the prescribing information for diltiazem for guidance on dose adjustment).
HMG-CoA Reductase Inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin [a] ↓ pravastatin [a] ↓ simvastatin [a]	Plasma concentrations of atorvastatin and pravastatin decreased. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose. A marked decrease in simvastatin plasma concentrations was seen when co-administered with efavirenz (see Table 9). Alternative statins should be considered.
Hormonal contraceptive:		A reliable method of barrier contraception must be used in addition to hormonal contraceptives.
Oral: Ethinyl estradiol/ Norgestimate	↓ active metabolites of norgestimate [a]	Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. The clinical significance of these effects is not known. No effect of ethinyl estradiol/norgestimate on efavirenz plasma concentrations was observed.
Implant: Etonogestrel	↓ etonogestrel	Decreased exposure of etonogestrel may be expected (CYP3A4 induction), and there have been post-marketing reports of contraceptive failure with etonogestrel in efavirenz -exposed patients.
Narcotic analgesic: Methadone	↓ methadone [a]	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

[a] For magnitude of interactions, see Tables 9 and 10.
[b] Not marketed in Canada

Table 7

Other Potentially Clinically Significant Drug Interactions With Efavirenz [a]	
Anticoagulants: Warfarin Acenocoumarol	Plasma concentrations and effects potentially increased or decreased by efavirenz. It is recommended that INR be monitored.
Anticonvulsants: Phenytoin Phenobarbital	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted. (See **WARNINGS AND PRECAUTIONS**.)
Antifungals: Ketoconazole	See **CONTRAINDICATIONS** for other antifungals. Drug interaction studies with efavirenz and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Anti-HIV protease inhibitors:	No pharmacokinetic data are available. (See Table 6.)

Other Potentially Clinically Significant Drug Interactions With Efavirenz [a]	
Saquinavir/ritonavir combination	
Calcium channel blockers: felodipine, nifedipine, verapamil	No data are available on the potential interactions of efavirenz with calcium channel blockers that are substrates of the CYP3A4 enzyme, other than diltiazem (see Table 6). The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the prescribing information for the calcium channel blocker).
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	When an immunosuppressant metabolized by CYP3A4 is administered with efavirenz, decreased exposure of the immunosuppressant may be expected due to CYP3A4 induction. 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.
Non-nucleoside reverse transcriptase inhibitors	No studies have been performed with other NNRTIs.

[a] This table is not all inclusive.

Other Drugs: Based on the results of drug interaction studies, no dosage adjustment of either efavirenz or the following coadministered drugs is recommended: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, nelfinavir, paroxetine, zidovudine and tenofovir disoproxil fumarate. (See **ACTION AND CLINICAL PHARMACOLOGY**; **Pharmacokinetics**, Tables 9 and 10.)

No dosage adjustment for lorazepam is recommended when coadministered with efavirenz.

Specific drug interaction studies have not been performed with efavirenz and NRTIs other than lamivudine and zidovudine. Clinically significant interactions would not be expected since the NRTIs are metabolized via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Drug-Food Interactions

Food increases the concentrations of efavirenz which may lead to an increase in frequency of adverse events. Therefore, it is recommended that Mylan-Efavirenz be taken on an empty stomach (See **DOSAGE AND ADMINISTRATION**; Recommended Dose and Dosage Adjustment and **ACTION AND CLINICAL PHARMACOLOGY**; **Pharmacokinetics, Effect of Food on Oral Absorption**).

Drug-Herb Interactions

St. John's Wort: Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products with efavirenz is contraindicated. Coadministration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including efavirenz, with St. John's wort is expected to substantially decrease NNRTI concentrations. Decreased concentrations may result in suboptimal levels of efavirenz and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

Drug-Laboratory Test Interactions

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 such as gas chromatography/mass spectrometry is recommended.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Mylan-Efavirenz must be given in combination with other antiretroviral medications.

Recommended Dose and Dosage Adjustment

Adults
The recommended dosage of efavirenz tablets in combination with other antiretroviral agents is 600 mg orally, once daily. It is recommended that Mylan-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 events (see **ACTIONS AND CLINICAL PHARMACOLOGY**; *Effect of Food on Oral Absorption*). Dosing at bedtime may improve the tolerability of nervous system symptoms (see **WARNINGS AND PRECAUTIONS**; **Neurologic** and **ADVERSE REACTIONS**).

Pediatric Patients and Adolescents

It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime. The recommended dosage of efavirenz in combination with other antiretroviral agents for patients 3 to 17 years of age is described in Table 8. There are insufficient data to recommend a dose in pediatric patients below 3 years of age or who weigh less than 13 kg. Mylan-Efavirenz tablets are not suitable for children weighing less than 40 kg. The recommended dosage of Mylan-Efavirenz for pediatric patients weighing greater than 40 kg is 600 mg, once daily.

Table 8
Pediatric Dose to be Administered Once Daily

Body Weight		Efavirenz Dose (mg)
kg	lbs	
≥40	≥88	600

Information is based on one study, ACTG 382. Patients were administered efavirenz in combination with nelfinavir and NRTIs.

Further dose adjustments may be required if other products are used concomitantly. (See **Pharmacokinetics**: **Drug-Drug Interactions** and **DRUG INTERACTIONS**.)
Renal Impairment

See **WARNINGS AND PRECAUTIONS**; **Special Populations**, **Renal Impairment**.

Hepatic Impairment

Mylan-Efavirenz is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) because of insufficient data to determine appropriate dosing. Caution should be exercised in administering Mylan-Efavirenz to patients with mild hepatic impairment because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience. See **WARNINGS AND PRECAUTIONS; Special Populations, Hepatic Impairment, Monitoring and Laboratory Tests, Liver enzymes** and **ACTION AND CLINICAL PHARMACOLOGY**; **Pharmacokinetics; Special Populations**.

Missed Dose

If a dose of Mylan-Efavirenz is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Center immediately.

Treatment of overdose with Mylan-Efavirenz (efavirenz) should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal should be used to aid removal of unabsorbed drug, as recommended in American College of Emergency Physicians guidelines. There is no specific antidote for overdose with Mylan-Efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions and a second patient experienced vomiting after taking twice the recommended dose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Efavirenz is a selective non-nucleoside reverse transcriptase (RT) inhibitor of human immunodeficiency virus type 1 (HIV- 1). Efavirenz is predominantly a non-competitive inhibitor of HIV-1 RT. HIV-2 RT and human cellular DNA polymerases α, β, γ and δ are not inhibited by concentrations of efavirenz well in excess of those achieved clinically (see **VIROLOGY**).
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 CYP2B*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see **WARNING AND PRECAUTION**).

Pharmacokinetics

Absorption

Peak efavirenz plasma concentrations were attained within 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.

In HIV-infected patients at steady-state, mean $C_{max,}$ mean $C_{min,}$ and mean AUC were dose proportional.

Effect of Food on Oral Absorption

Tablets: Administration of a single 600 mg dose of 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**; **Recommended Dose and Dosage Adjustment**).

Distribution

Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (N=9), efavirenz cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration; approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism

In vivo and *in vitro* studies 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.

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism.

Elimination

Efavirenz has a long terminal half-life of 52-76 hours after single doses and 40-55 hours after multiple doses. 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 radiolabelled drug was in the form of metabolites. Efavirenz accounted for the majority of the total radioactivity measured in feces (see **PHARMACOLOGY**; **Pharmacokinetics** for more detail.)

Special Populations

Hepatic Impairment

In a multiple-dose efavirenz PK study (600 mg daily), the mean Cmax and mean AUC of efavirenz in patients with mild hepatic impairment (Child-Pugh Class A, n=6) were 20.3 ± 15.5 μM (mean ± SD) and 351 ± 336.9 μM•h (mean ± SD), respectively, compared with those in controls (n=6; Cmax=28.4 ± 27.35 μM, AUC=506 ± 581 μM•h). There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh Class B or C) affects efavirenz pharmacokinetics (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions

Tables 9 and 10 show drug-drug interactions of efavirenz with various co-administrated drugs and their pharmacokinetic profiles (see **DRUG INTERACTIONS**).

Table 9
Effect of Efavirenz on Coadministered Drug Plasma C_{max} , AUC and C_{min}

Coadministered Drug Class: Drug Name	Dose	Efavirenz Dose	Coadministered Drug (Mean % change)		
			Cmax	AUC	Cmin
Antiretroviral agents					
Protease inhibitor:					
Atazanavir	400 mg daily x 20 days	600 mg d 7-20	↓ 59%	↓ 74%	↓ 93%
Atazanavir/ritonavir	400 mg daily d 1-6, then 300 mg daily d 7-20 with ritonavir 100 mg daily and a light meal	600 mg daily 2 h after atazanavir and ritonavir d 7-20	↑ 14%[a]	↑ 39%[a]	↑ 48%[a]
	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 d 11-24 (pm)	↑ 17%	↔	↓ 42%

Coadministered Drug Class: Drug Name	Dose	Efavirenz Dose	Coadministered Drug (Mean % change)		
Protease inhibitor: Indinavir	1000 mg q8h x 10 days after morning dose after afternoon dose after evening dose	600 mg x 10 days	↔[b] ↓ 29%[b]	↓ 37%[b] ↓ 46%[b]	↓ 52%[b] ↓ 57%[b]
Protease inhibitor: Indinavir / ritonavir	Indinavir 800 mg + ritonavir 100 mg q12h d 1-29	600 mg d 15-29	↓ 17%[e]	↓ 25%[e]	↓ 50%[e]
Protease inhibitor: Lopinavir/ritonavir	400/100 mg capsule q12h x 9 days 600/150 mg tablet q12h x 10 days with efavirenz compared to 400/100 mg q12h alone	600 mg x 9 days 600 mg x 9 days	↔[c] ↑ 36%	↓ 19%[c] ↑ 36%	↓ 39%[c] ↑ 32%
CCR5 co-receptor antagonist: Maraviroc	100 mg bid	600 mg	↓ 51%	↓ 45%	↓ 45%
Integrase strand transfer inhibitor: Raltegravir	400 mg single dose	600 mg	↓ 36%	↓ 36%	↓ 21%
Protease inhibitor: Nelfinavir Metabolite AG-1402	750 mg q8h x 7 days	600 mg x 7 days	↑ 21% ↓ 40%	↑ 20% ↓ 37%	↔ ↓ 43%
Protease inhibitor: Ritonavir	500 mg q12h x 8 days after AM dose after PM dose	600 mg x 10 days	↑ 24% ↔	↑ 18% ↔	↑ 42% ↑ 24%
Protease inhibitor: Saquinavir (SGC) [g]	1200 mg q8h x 10 days	600 mg x 10 days	↓ 50%	↓ 62%	↓ 56%
Nucleoside reverse transcriptase inhibitor: Lamivudine	150 mg q12h x 14 days	600 mg x 14 days	↔	↔	↑ 265%
Nucleoside reverse transcriptase inhibitor: Zidovudine	300 mg q12h x 14 days	600 mg x 14 days	↔	↔	↑ 225%
Nucleotide reverse transcriptase inhibitor: Tenofovir disoproxil fumarate	300 mg daily	600 mg x 14 days	↔	↔	↔
Hepatitis C antiviral agents					

Coadministered Drug Class: Drug Name	Dose	Efavirenz Dose	Coadministered Drug (Mean % change)		
NS5B polymerase inhibitor /NS5A inhibitor: Sofosbuvir/velpatasvir[i]	400 mg once daily / 100 mg once daily	600 mg once daily	↑ 38% / ↓ 47%	↔/ ↓ 53%	NA/ ↓ 57%
Other agents					
Anticonvulsant: Carbamazepine	200 mg daily x 3 days, 200 mg bid x 3 days, then 400 mg daily x 29 days	600 mg x 14 days	↓ 20%	↓ 27%	↓ 35%
Epoxide metabolite			↔	↔	↓ 13%
Antidepressant: Buproprion	150 mg single dose (sustained-release)	600 mg x 14 days	↓ 34%	↓ 55%	NA
Hydroxybupropion			↑ 50%	↔	NA
Antidepressant: Paroxetine	20 mg daily x 14 days	600 mg x 14 days	↔	↔	↔
Antidepressant: Sertraline	50 mg daily x 14 days	600 mg x 14 days	↓ 29%	↓ 39%	↓ 46%
N desmethylsertraline			↓ 17%	↓ 20%	↓ 20%
Antifungal: Fluconazole	200 mg x 7 days	400 mg x 7 days	↔	↔	↔
Antifungal: Itraconazole	200 mg q12h x 28 days	600 mg x 14 days	↓ 37%	↓ 39%	↓ 44%
Hydroxyitraconazole			↓ 35%	↓ 37%	↓ 43%
Antifungal: Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg x 10 and 20 days	↓ 45%	↓ 50%	NA
Antifungal: Voriconazole	400 mg q12h d -1 200 mg q12h d 2-9	400 mg x 9 days	↓ 61%	↓ 77%	NA
	300 mg po q12h d 2-7	300 mg x 7 days	↓ 36%[f]	↓ 55%[f]	NA
	400 mg po q12h d 2-7	300 mg x 7 days	↑ 23%[f]	↔[f]	NA
Anti-infective: Azithromycin	600 mg single dose	400 mg x 7 days	↑ 22%	↔	NA
Anti-infective: Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	↓ 26%	↓ 39%	↓ 53%
14-OH metabolite			↑ 49%	↑ 34%	↑ 26%
Antimalarial: Artemether[h]	80/480 mg bid x 3 days before and during efavirenz coadministration	600 mg x 26 days	↓ 21%	↓ 51%	NA
dihydroartemisinin (active metabolite of artemether)[h]			↓ 38%	↓ 46%	NA
lumefantrine[h]			↔	↓ 21%	NA
Antimycobacterial: Rifabutin	300 mg daily x 14 days	600 mg x 14 days	↓ 32%	↓ 38%	↓ 45%
25-0-desacetylrifabutin			↓49%[d]	↓ 74%[d]	NA

Coadministered Drug Class: Drug Name	Dose	Efavirenz Dose	Coadministered Drug (Mean % change)		
Anxiolytic: Lorazepam	2 mg single dose	600 mg x 10 days	↑ 16%	↔	NA
Calcium channel blocker: Diltiazem Desacetyl diltiazem N-monodesmethyl diltiazem	240 mg x 21 days	600 mg x 14 days	↓ 60% ↓ 64% ↓ 28%	↓ 69% ↓ 75% ↓ 37%	↓ 63% ↓ 62% ↓ 37%
H1 receptor antagonist: Cetirizine	10 mg single dose	600 mg x 10 days	↓ 24%	↔	NA
HMG-CoA reductase inhibitor: Atorvastatin Total active (including metabolites)	10 mg daily x 4 days	600 mg x 15 days	↓ 14% ↓ 15%	↓ 43% ↓ 32%	↓ 69% ↓ 48%
HMG-CoA reductase inhibitor: Pravastatin	40 mg daily x 4 days	600 mg x 15 days	↓ 32%	↓ 44%	↓ 19%
HMG-CoA reductase inhibitor: Simvastatin Total active (including metabolites)	40 mg daily x 4 days	600 mg x 15 days	↓ 72% ↓ 68%	↓ 68% ↓ 60%	↓ 45% NA
Narcotic analgesic: Methadone	Stable maintenance 35-100 mg daily	600 mg x 14-21 days	↓ 45%	↓ 52%	NA
Oral contraceptive: Ethinyl estradiol/ Norgestimate Ethinyl estradiol Norelgestromin Levonorgestrel	0.035 mg/ 0.25 mg x 14 days	600 mg x 14 days	 ↔ ↓ 46% ↓ 80%	 ↔ ↓ 64% ↓ 83%	 ↔ ↓ 82% ↓ 86%

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

[a] Compared with atazanavir 400 mg daily alone.

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

[c] Values are for lopinavir. $_{Cmin}$ of lopinavir was significantly decreased by 39%. $_{Cmax}$ and AUC of lopinavir were decreased by 3% and 19% respectively (not significant). The pharmacokinetics of ritonavir 100 mg q12h are unaffected by concurrent efavirenz.

[d] Based on arithmetic mean values.

[e] Compared to indinavir 800 twice daily given with ritonavir 100 mg twice daily without efavirenz. The geometric Cmin for indinavir (0.33 mg/L) when given with ritonavir and efavirenz was higher than the mean historical Cmin (0.15 mg/L) when indinavir was given alone at 800 mg every 8 hours. When efavirenz 600 mg once daily was given with indinavir/ritonavir 800/100 mg twice daily in HIV-1-infected patients (n=6), the pharmacokinetics of indinavir and efavirenz were generally comparable to these data from uninfected volunteers.

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

[g] SGC Soft Gelatin Capsule

[h] Not marketed in Canada

[i] Administered as ATRIPLA (efavirenz, emtricitabine and tenofovir DF fixed-dose combination)

Table 10

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

Coadministered Drug Class: Drug Name	Dose	Efavirenz Dose	Efavirenz (Mean % change)

			Cmax	AUC	Cmin
Antiretroviral agents					
Protease inhibitor: Atazanavir	400 mg daily x 20 days	600 mg d 7-20	↔	↔	NA
Protease inhibitor: Indinavir	800 mg q8h x 14 days	200 mg x 14 days	↔	↔	↔
Protease inhibitor: Lopinavir/ritonavir	400/100 mg q12h x 9 days	600 mg x 9 days	↔	↓ 16%	↓ 16%
Protease inhibitor: Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	↓ 12%	↓ 12%	↓ 21%
Protease inhibitor: Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	↑ 14%	↑ 21%	↑ 25%
Protease inhibitor: Saquinavir (SGC) [b]	1200 mg q8h x 10 days	600 mg x 10 days	↓ 13%	↓ 12%	↓ 14%
Nucleotide reverse transcriptase inhibitor: Tenofovir disoproxil fumarate	300 mg daily	600 mg x 14 days	↔	↔	↔
Hepatitis C antiviral agents					
NS5B polymerase inhibitor /NS5A inhibitor: Sofosbuvir/velpatasvir[d]	400 mg / 100 mg daily	600 mg daily	↔	↔	↔
Other agents					
Antacid: Aluminum hydroxide 400 mg Magnesium hydroxide 400 mg, + simethicone 30 mg	30 mL single dose	400 mg single dose	↔	↔	NA
Anticonvulsant: Carbamazepine	200 mg daily x 3 days, 200 mg bid x 3 days, then 400 mg daily x 15 days	600 mg x 35 days	↓ 21%	↓ 36%	↓ 47%
Antidepressant: Paroxetine	20 mg daily x 14 days	600 mg x 14 days	↔	↔	↔
Antidepressant: Sertraline	50 mg daily x 14 days	600 mg x 14 days	↑ 11%	↔	↔
Antifungal: Fluconazole	200 mg x 7 days	400 mg x 7 days	↔	↑ 16%	↑ 22%
Antifungal: Itraconazole	200 mg q12h x 14 days	600 mg x 28 days	↔	↔	↔
Antifungal: Voriconazole	400 mg q12h d-1 200 mg q12h d 2-9 300 mg po q12h d 2-7 400 mg po q12h d 2-7	400 mg x 9 days 300 mg x 7 days 300 mg x 7 days	↑ 38% ↓ 14% [a] ↔[a]	↑ 44% ↔[a] ↑ 17% [a]	NA NA NA
Anti-infective: Azithromycin	600 mg single dose	400 mg x 7 days	↔	↔	↔

Coadministered Drug Class: Drug Name	Dose	Efavirenz Dose	Efavirenz (Mean % change)		
			Cmax	AUC	Cmin
Anti-infective: Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	↑ 11 %	↔	↔
Antimycobacterial: Rifabutin	300 mg daily x 14 days	600 mg x 14 days	↔	↔	↓ 12%
Antimycobacterial: Rifampin	600 mg x 7 days	600 mg x 7 days	↓ 20%	↓ 26%	↓ 32%
Calcium channel blocker: Diltiazem	240 mg x 14 days	600 mg x 28 days	↑ 16 %	↑ 11%	↑ 13%
H_1 receptor antagonist: Cetirizine	10 mg single dose	600 mg x 10 days	↔	↔	↔
H_2 receptor antagonist: Famotidine	40 mg single dose	400 mg single dose	↔	↔	NA
HMG-CoA reductase inhibitor: Atorvastatin	10 mg daily x 4 days	600 mg x 15 days	↔	↔	↔
HMG-CoA reductase inhibitor: Pravastatin	40 mg daily x 4 days	600 mg x 15 days	↔	↔	↔
HMG-CoA reductase inhibitor: Simvastatin	40 mg daily x 4 days	600 mg x 15 days	↓ 12%	↔	↓ 12%

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%
[a] Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).
[b] SGC Soft Gelatin Capsule
[c] Not marketed in Canada
[d] Administered as ATRIPLA (efavirenz, emtricitabine and tenofovir DF fixed-dose combination

STORAGE AND STABILITY

Mylan-Efavirenz (efavirenz tablets) should be stored between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

Mylan-Efavirenz (efavirenz) is available as tablets for oral administration.

Composition and Packaging

Tablets 600 mg are yellow, film coated, capsule shaped, biconvex tablets, debossed with “M” on one side of the tablet and “EZ6” on the other side. Available in bottles containing 30 tablets and 100 tablets.

Tablets contain 600 mg of efavirenz and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, sodium lauryl sulfate, hydroxypropyl cellulose, lactose

monohydrate, and magnesium stearate. The film coating contains hypromellose, iron oxide red, iron oxide yellow, polyethylene glycol and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

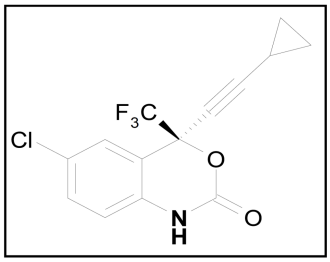
Drug Substance

Proper Name: Efavirenz

Chemical Name: (S) -6- chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one.

Molecular Formula: $C_{14}H_9ClF_3NO_2$

Molecular Mass: 315.68 g/mol

Structural Formula: 

Physicochemical Properties

Description: Efavirenz is a white to slightly pink crystalline powder.

Solubility: Efavirenz is practically insoluble in water at a concentration of <10 µg/mL.

Partition coefficient: The (octanol/water) partition coefficient is determined to be P=5.4.

Melting point: The melting point is 137.2 ± 1.4°C.

pKa: The pKa is 10.2.

CLINICAL TRIALS

Comparative Bioavailability Studies

A pivotal, double blind, balanced, randomized, single oral dose, two-treatment, two-period, two-sequence, two way crossover bioequivalence study of Mylan-Efavirenz (efavirenz) 600 mg (Mylan Pharmaceuticals ULC) and SUSTIVA® (efavirenz) 600 mg tablets (Bristol-Myers Squibb Canada) was performed in healthy, adult, Indian male subjects (n=30) under fasting conditions.

The results of the bioequivalence study are tabulated below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Efavirenz (1 × 600 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90 % Confidence Interval
$AUC_{(0-72)}$ (µg·h/mL)	69.269 71.195 (24.98)	60.838 63.997 (33.96)	113.86	103.96 to 124.70
C_{max} (µg/mL)	3.476 3.581 (26.45)	3.002 3.110 (27.27)	115.78	102.30 to 131.04
T_{max}§ (h)	4.50 (1.50-5.50)	3.75 (1.00-7.00)		
$T_{½}$€ (h)	57.30 (81.49)	52.68 (41.82)		

* Mylan-Efavirenz, 600mg (efavirenz) Mylan Pharmaceuticals ULC, Toronto, Canada.

† ^{Pr}Sustiva, 600mg (Bristol-Myers Squibb Canada) was purchased in Canada.

§ Expressed as the median (range) only.

€ Expressed as the arithmetic mean (CV%) only.

Clinical Studies

The principal efficacy analyses compared the durability of virologic suppression by assessing the proportion of subjects responding to treatment with HIV RNA less than the assay limit. Plasma HIV RNA levels were quantified using the AMPLICOR HIV-1 MONITOR assay. The standard assay with a limit of 500 copies/mL was used in study 364. In studies 006 and 020, standard assay with a limit of 400 copies/mL and ultrasensitive assay with a limit of 50 copies/mL were used. During study 006, version 1.5 of the AMPLICOR assay was introduced in Europe to enhance detection of non-clade B virus.

The secondary analyses compared the magnitude and durability of the change in plasma HIV-RNA levels and CD4 cell counts from baseline.

In the analysis, patients who terminated the study early for any reason or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit

of assay quantification were considered to have HIV-RNA above 400 copies/mL, or above 50 copies/mL in the case of the Ultrasensitive assay, at the missing time points.

Study 006: Efavirenz + indinavir or efavirenz + zidovudine + lamivudine versus indinavir + zidovudine + lamivudine in antiretroviral-naive or NRTI-experienced (lamivudine-naive) patients:

Study 006 is a randomized open label trial to evaluate the plasma HIV-RNA suppression achieved by efavirenz in combination with either indinavir (IDV) or with zidovudine (ZDV) + lamivudine (3TC) compared to indinavir plus zidovudine + lamivudine in HIV-infected patients naive to lamivudine, protease inhibitors and NNRTIs. Study 006 was designed as an equivalency trial. Patients were randomized to one of three treatment regimens: efavirenz (600 mg daily) + indinavir (1000 mg q8h) or efavirenz (600 mg daily) + zidovudine (300 mg q12h) + lamivudine (150 mg q12h) versus indinavir (800 mg q8h) + zidovudine (300 mg q12h) + lamivudine (150 mg q12h). The 1266 patients enrolled in the study had a mean age of 36.5 years (range 18-81); 60% were caucasian and 83% were male. The mean baseline CD4 count was 341 cells/mm^3, mean HIV RNA plasma level was 4.8 log10 copies/mL. Forty-eight and 168 week data are presented in Table 11. Through 48 and 168 weeks of therapy, increases in CD4 cell counts were not significantly different between treatment arms.

Table 11
Study 006 - Summary of Key Efficacy Results - Week 48 and Week 168

Treatment Regimen	**Efavirenz + IDV**		**Efavirenz + ZDV + 3TC**		**IDV + ZDV + 3TC**	
Total N Randomized	N = 429		N = 422		N = 415	
Patients with Plasma HIV-RNA <400 copies/mL - Amplicor Assay						
Responder / Evaluable (%)						
	Week 48	Week 168	Week 48	Week 168	Week 48	Week 168
TLOVR[a]	246 / 429 (57)	171 / 429 (40)	293 / 422 (69)	203 / 422 (48)	206 / 415 (50)	123 / 415 (30)
TTF[b]	234 / 429 (55)	161 / 429 (38)	270 / 422 (64)	190 / 422 (45)	186 / 415 (45)	114 / 415 (27)
VR-OC	249 / 294 (85)	172 / 181 (95)	300 / 317 (95)	216 / 228 (95)	216 / 253 (85)	127 / 140 (91)
Difference Estimate (97.5% CI) at Week 168						
Treatment Regimen	efavirenz+IDV - IDV+ZDV+3TC			efavirenz+ZDV+3TC - IDV+ZDV+3TC		
TLOVR[a]	10.2 (2.9, 17.6) p = 0.0018 [c]			18.5 (10.9, 26.0) p < 0.0001 [d]		
TTF[b]	10.1 (2.8, 17.3) p = 0.0018 [c]			17.6 (10.1, 25.0) p < 0.0001 [d]		
VR-OC	4.3 (-2.1, 10.7) p = 0.1293 [c]			4.0 (-2.0, 10.1) p = 0.1365 [d]		
Patients with Plasma HIV-RNA <50 copies/mL - Ultrasensitive Assay						
Responder / Evaluable (%)						
	Week 48	Week 168	Week 48	Week 168	Week 48	Week 168
TLOVR[a]	209 / 429 (49)	134 / 429 (31)	268 / 422 (64)	180 / 422 (43)	177 / 415 (43)	96 / 415 (23)
TTF[b]	204 / 429 (48)	128 / 429 (30)	255 / 422 (60)	169 / 422 (40)	166 / 415 (40)	89 / 415 (21)
VR-OC	214 / 294 (73)	158 / 181 (87)	273 / 317 (86)	207 / 228 (91)	189 / 253 (75)	113 / 140 (81)
Difference Estimate (97.5% CI) at Week 168						
Treatment Regimen	efavirenz+IDV - IDV+ZDV+3TC			efavirenz+ZDV+3TC - IDV+ZDV+3TC		
TLOVR[a]	8.1 (1.2, 15.0) p = 0.0082 [c]			19.5 (12.2, 26.8) p < 0.0001 [d]		
TTF[b]	8.4 (1.6, 15.1) p = 0.0053 [c]			18.6 (11.4, 25.8) p < 0.0001 [d]		
VR-OC	6.6 (-2.6, 15.7) p = 0.1070 [c]			10.1 (2.0, 18.2) p = 0.0053 [d]		
Change from Baseline - HIV RNA level (log10 c/mL)						
	Week 48	Week 168	Week 48	Week 168	Week 48	Week 168
N Mean (se)	289 -2.65 (0.055)	165 -2.98 (0.058)	310 -2.91 (0.041)	210 -3.07 (0.047)	251 -2.65 (0.059)	133 -2.88 (0.068)

Median	-2.84	-3.08	-2.94	-3.09	-2.82	-2.96
Change from Baseline - CD4 Cell Counts (cells/mm^3)						
	Week 48	Week 168	Week 48	Week 168	Week 48	Week 168
N	256	158	279	205	228	129
Mean (se)	191 (9.4)	319 (14.9)	190 (10.1)	329 (14.4)	180 (11.6)	329 (21.1)
Median	170	300	179	292	157	292

TLOVR = Time to Loss of Virologic Response
A minimum of two consecutive HIV RNA measurements < LOQ maintained through end of study without intervening confirmed rebounds or treatment discontinuations. If the last measurement on-study was > LOQ, the subject was considered a failure for that visit. Deaths, loss to follow-up, and changes in antiretroviral therapy also counted as failure in the TLOVR algorithm.

TTF = Time to Treatment Failure
Loss of HIV RNA suppression (confirmed RNA ≥ 400 copies/mL), development of a CDC Class C AIDS-defining event, treatment discontinuation or start of alternative HIV treatment after having two consecutive HIV RNA determinations < LOQ, or failure to virologically suppress or failure to receive study medication after randomization up to the reported visit week.

VR-OC = Virologic Response - Observed Cases
Classified subjects who remained on treatment according to a single HIV RNA measurement, either < LOQ or ≥ LOQ closest to the scheduled visit and within a predefined visit window. Only those subjects who remained on treatment at the time of their visit week were included. Subjects with HIV RNA ≥ LOQ were considered failures. Subjects who remained on treatment and were missing a measurement were classified as responders only if their immediately previous and subsequent viral loads met the VR-OC criteria for response.

[a] Proportion responding using the TLOVR definition of response
[b] Proportion responding using the TTF definition of response
[c] Statistical difference between efavirenz + IDV and IDV + ZDV + 3TC, at Week 168
[d] Statistical difference between efavirenz + ZDV + 3TC and IDV +ZDV + 3TC, at Week 168

HIV-RNA status and the reasons for discontinuations of randomized treatment are summarized (Table 12).

Table 12
Outcomes of Randomized Treatment Through 48 and 168 Weeks, Study 006

Outcome	Efavirenz + IDV n = 429		Efavirenz + ZDV + 3TC n=422		IDV + ZDV + 3TC n = 415	
	Week 48	Week 168	Week 48	Week 168	Week 48	Week 168
Responder[a]	57%	40%	69%	48%	50%	30%
Virologic failure[b]	15%	19%	6%	12%	13%	17%
Discontinued for adverse events	5%	8%	7%	8%	15%	20%
Discontinued for other reasons[c]	23%	32%	17%	31%	22%	32%
CD4 + cell count (cells/mm^3)						
Observed subjects (n)	256	158	279	205	228	129
Mean change from baseline	191	319	190	329	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.

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.

Study ACTG 364: Efavirenz in combination with nelfinavir (NFV) in NRTI-experienced patients:

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 and ninety-five HIV-infected patients (mean age 41 years [range 18-76], 74% Caucasian, 88% male) received NRTIs in combination with efavirenz (600 mg daily), or nelfinavir (750 mg TID), or efavirenz (600 mg daily) plus nelfinavir in a randomized double-blinded manner. Upon entry into the study, all patients were assigned a new open label NRTIS regimen, which was dependent on their previous NRTIS treatment experience. Through 48 weeks of therapy, there was no significant difference in the mean CD4 cell count between the treatment arm. Overall efficacy results are summarized in Table 13.

Table 13
ACTG 364- Summary of Key Efficacy Results -Week 48

	NFV + 2NRTIs	**Efavirenz + 2NRTIs**	**NFV + Efavirenz + 2NRTIs**
Total N Randomized	66	65	65
Patients with Plasma HIV-RNA <500 copies/mL (95% Cl) - Amplicor Assay			
LOCF	23/66 (34.8%) (23.4, 46.3)	39/65 (60.0%) ‡ (48.1, 71.9)	49/65 (75.4%)* # ¶ (64.9, 85.9)
NC=F	19/63 (30.2%) (18.8, 41.5)	36/62 (58.1%) (45.8, 70.3)	45/64 (70.3%)* ‡ ¶ (59.1, 81.5)
Mean Change from Baseline - Log_{10} Transformed Plasma HIV-RNA (SEM)			
Amplicor (LOCF)	-0.45 (0.09)† N = 66	-0.72 (0.09)† N = 65	-0.87 (0.10)† N = 62
Mean Change from Baseline - CD4 Counts (SEM)			
LOCF	93.8 (13.6)† N = 66	113.8 (21.0)† N = 65	107.4 (17.9)† N = 63

* Statistically significant difference between NFV+2NRTIs and NFV+efavirenz+2NRTIs ($p \leq 0.05$)
# Statistically significant difference between efavirenz+2NRTIs and NFV+efavirenz+2NRTIs ($p \leq 0.05$)
† Statistically significant change from baseline ($p \leq 0.05$)
‡ Statistically significant difference between NFV+2 NRTIs and efavirenz+2NRTIs ($p \leq 0.05$).
¶ Statistically significant difference among treatment groups.
LOCF: This analysis is based on the last obtained plasma HIV-RNA or CD4 cell count measurement for each patient randomized into the study (Intent-to-Treat: Last Observation Carried Forward analysis). NC=F: Noncompleter = Failure. In this analysis, any patient with viral load above quantifiable levels using a specified assay, or whose viral load data are missing at some time point of the analysis, is considered to be a virologic failure (i.e., HIV-RNA ≥500 copies/mL using the Roche Amplicor™ assay), unless the patient's viral load measurements both before and after the missing data point are below the assay limit of quantification.
CI: Confidence Interval

HIV-RNA status and the reasons for discontinuations of randomized treatment are summarized (Table 14).

Table 14
Study ACTG 364 - Outcomes of Randomized Treatment Through 48 Weeks

Outcome	Efavirenz + NFV + NRTIs N=65	Efavirenz + NRTIs N=65	NFV + NRTIs N=66
HIV-RNA <500 copies/mL[1]	70%	58%	30%
HIV-RNA ≥500 copies/mL[2,3]	13%	27%	60%
Discontinuations for Adverse Events[3]	3%	3%	5%
Discontinuations for Other Reasons[3]	9%	2%	0%
On Treatment with Missing HIV-RNA Value[3]	5%	10%	5%
Total	100%	100%	100%

[1] Corresponds to rates at 48 weeks in Table 13
[2] Includes discontinuation due to virologic failure at or before 48 weeks
[3] Treatment Failure in the Analysis

Study 020: Protease Inhibitor + Two NRTIs with/without efavirenz in NRTI-experienced patients:

Study 020 was a randomized, double-blind, placebo-controlled 24-week study in NRTI--experienced, protease inhibitor and NNRTI-naive patients designed to compare quadruple therapy consisting of efavirenz + indinavir + 2 nucleoside analogue reverse transcriptase inhibitors versus triple therapy consisting of indinavir + 2 NRTIs at 24 weeks of treatment. Patients were randomized to receive either efavirenz (600 mg daily) + indinavir (1000 mg q8h) + 2 NRTIs or indinavir (800 mg q8h) + 2 NRTIs. Sixty-seven percent of the 327 patients (mean age 38.5 years [range 20-69], 52% Caucasian, 83% male) changed their NRTI regimen at study initiation. Mean baseline CD4 count was 328 cells/mm^3, and mean HIV-RNA plasma level was 4.41 $\log_{10}$ copies/mL. Through 24 weeks of therapy, there was no significant difference in the mean CD4 cell count between the treatment arms. Mean increases in CD4 cell count at 24 weeks were 104 cells/mm^3 for patients treated with efavirenz+IDV+NRTIs, and 77 cells/mm^3 for patients treated with IDV+NRTIs. The Noncompleter=Failure analysis at 24 weeks showed no difference between the treatment groups using a cutoff of 400 copies/mL and a significant difference between treatment groups using a cutoff of 50 copies/mL. Efficacy results are summarized in Table 15.

Table 15
Study 020 - Summary of Key Efficacy Results - Week 24

	Efavirenz + NRTIs	IDV + NRTIs
Total N Randomized	157	170
Patients with Plasma HIV-RNA <400 copies/mL (95% CI) - Amplicor Assay		
LOCF	107/157 (68.2%)* (60.5, 75.8)	89/170 (52.4%) (44.6, 60.2)
NC=F	93/156 (59.6%) (51.6, 67.6)	86/169 (50.9%) (43.1, 58.7)
Observed	93/112 (83.0%)* (75.6, 90.4)	86/132 (65.2%) (56.6, 73.7)

	Efavirenz + NRTIs	IDV + NRTIs
Total N Randomized	157	170
Patients with Plasma HIV-RNA <50 copies/mL (95% Cl) - Ultrasensitive Assay		
LOCF	79/156 (50.6%)* (42.5, 58.8)	65/168 (38.7%) (31.0, 46.4)
NC+F	77/156 (49.4%)* (41.2, 57.5)	63/168 (37.5%) (29.9, 45.1)
Observed	77/112 (68.8%)* (59.7, 77.8)	63/132 (47.7%) (38.8, 56.6)
Mean Change from Baseline - Log_{10} Transformed Plasma HIV-RNA (SEM)		
Amplicor (LOCF)	-1.45 (0.08)* † N = 147	-1.12 (0.08)† N = 158
Ultrasensitive** (LOCF)	2.25 (0.10)* † N = 120	-1.72 (0.11)†
Mean Change from Baseline -CD4 Counts (SEM)		
LOCF	104.4 (9.1)* † N = 151	76.9 (9.9)† N = 158

* Statistically significant difference between treatments ($p \leq 0.05$)

† Statistically significant change from baseline ($p \leq 0.05$)

** Ultrasensitive Assay is an unvalidated experimental method.

LOCF: This analysis is based on the last obtained plasma HIV-RNA or CD4 cell count measurement for each patient randomized into the study (Intent-to-Treat: Last Observation Carried Forward analysis).

NC=F: Noncompleter = Failure. In this analysis, any patient with viral load above quantifiable levels using a specified assay, or whose viral load data are missing at some time point of the analysis, is considered to be a virologic failure (i.e., HIV-RNA ≥400 copies/mL using the Roche Amplicor™ assay), unless the patient's viral load measurements both before and after the missing data point are below the assay limit of quantification.

Observed: Analysis is based on all data available at the specified time point (on-treatment analysis). Missing data is not accounted for in this analysis.

CI: Confidence Interval

HIV-RNA status and the reasons for discontinuations of randomized treatment are summarized (Table 16).

Table 16
Study 020 - Outcomes of Randomized Treatment Through 24 Weeks

Outcome	Efavirenz + IDV + NRTIs N = 157	IDV + NRTIs N = 170
HIV-RNA <400 copies/mL [<50 copies/mL]	60% [51%]	51% [39%]
HIV-RNA ≥400 copies/mL [≥50 copies/mL][1,2]	11% [20%]	26% [38%]
Discontinuations for Adverse Events[2]	11%	5%
Discontinuations for Other Reasons[2]	18%	16%
On Treatment with Missing HIV-RNA Value[2]	0%	2%
Total	100%	100%

[1] Includes discontinuation due to virologic failure at or before 48 weeks

[2] Treatment Failure in the Analysis

DETAILED PHARMACOLOGY

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. Time to peak plasma concentrations (3-5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6-10 days.

In HIV-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. In 35 patients receiving efavirenz 600 mg daily, mean steady-state C_{max} was 12.9 μM, mean steady state C_{min} was 5.6 μM, and mean AUC was 184 μM/h.

Effect of Food on Oral Absorption

Tablets: Administration of a single 600 mg dose of 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**.)

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 CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. *In vitro* studies have shown that efavirenz inhibited P450 isozymes 2C9, 2C19, and 3A4 with K_i values (8.5-17.0 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.

Efavirenz plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isozyme. The clinical implications of such an association are unknown;

however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce P450 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). The degree of CYP3A4 induction is expected to be similar between a 400 mg and 600 mg dose of efavirenz based on pharmacokinetic interaction studies in which daily 400 mg or 600 mg efavirenz doses in combination with indinavir did not appear to cause any further reduction of indinavir AUC compared to a 200 mg dose of efavirenz.

Elimination

Efavirenz has a long 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-labelled 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 radiolabelled drug was in the form of metabolites. Efavirenz accounted for the majority of the total radioactivity measured in feces.

Demographics

The pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the ethnic groups studied.

Hepatic Enzyme Induction

Efavirenz has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A4 and CYP2B6. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isozymes 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. The effects on CYP3A4 activity are expected to be similar between 200 mg, 400 mg and 600 mg doses of efavirenz. Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19 and 3A4 isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A4 activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

VIROLOGY

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Efavirenz is predominantly a non-competitive inhibitor of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α, β, γ and δ are not inhibited by concentrations of efavirenz well in excess of those achieved clinically.

***In vitro* HIV Susceptibility:** The clinical significance of *in vitro* susceptibility of HIV-1 to efavirenz has not been established. The *in vitro* antiviral activity of efavirenz was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures enriched from PBMCs. The 90-95% inhibitory concentration (IC_{90-95}) of efavirenz for wild type laboratory adapted strains and clinical isolates ranged from 1.7 to ≤ 25nM. EFV demonstrated antiviral activity against most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses. EFV demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine (DLV) and nevirapine (NVP), NRTIs (abacavir, didanosine, emtricitabine, lamivudine [LAM], stavudine, tenofovir, zalcitabine, zidovudine [ZDV]), PIs (amprenavir, indinavir [IDV], lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. EFV demonstrated additive to antagonistic antiviral activity *in vitro* with atazanavir. EFV 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: HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in IC_{90}) compared to baseline can emerge rapidly in cell culture in the presence of drug. Genotypic characterization of these viruses identified mutations resulting in single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in RT. Phenotypic (N=26) changes in evaluable HIV- 1 isolates and genotypic (N=104) changes in plasma virus from selected patients treated with efavirenz in combination with IDV, or with ZDV plus lamivudine were monitored. Clinical isolates with reduced susceptibility in cell culture to efavirenz have been obtained. One or more RT mutations at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190 and 225, and 227 were observed in all 102 of 104 patients with a frequency of at least 9% compared to baseline. The mutation at RT amino acid position 103 (lysine to asparagine) was the most frequently observed (≥90%). A mean loss in susceptibility (IC_{90}) to efavirenz of 47-fold was observed in 26 clinical isolates. Five clinical isolates were evaluated for both genotypic and phenotypic changes from baseline. Decreases in efavirenz susceptibility (range from 9 to >312-fold increase in IC_{90}) were observed for these isolates in cell culture compared to baseline. All 5 isolates possessed at least one of the efavirenz-associated RT mutations. The clinical relevance of phenotypic and genotypic changes associated with efavirenz therapy has not been established. 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 EFV susceptibility in cell culture with a median 88-fold change in EFV susceptibility (IC_{50} value) from reference. The most frequent NNRTI mutation to develop in these patient isolates was K103N (54%). Other NNRTI mutations that developed included L100I (7%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%).

Cross-Resistance: Rapid emergence of HIV- 1 strains that are cross-resistant to non-nucleoside RT inhibitors has been observed in cell culture. Thirteen clinical isolates previously characterized as efavirenz-resistant were also phenotypically resistant to nevirapine and delavirdine in cell culture compared to baseline. DLV- and/or NVP-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 EFV in cell culture. Clinically derived ZDV-resistant HIV-1 isolates tested in cell culture retained susceptibility to efavirenz. Cross-resistance between efavirenz and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

TOXICOLOGY

Acute Toxicity

The oral Minimum Lethal Dose (MLD) of efavirenz in female rats ranged from 250 mg/kg to 500 mg/kg, whereas the oral MLD of efavirenz in male rats was 1000 mg/kg. The most prominent clinical signs attributed to efavirenz treatment in rats were ataxia and decreased motor activity, and were observed, in general, at doses ≥250 mg/kg. The MLD in female and male rats given intraperitoneal injections of efavirenz was 250 mg/kg and 500 mg/kg, respectively. The MLD in mice given intraperitoneal injections of efavirenz was similar to that in rats (250 mg/kg in both male and female mice).

Efavirenz Toxicokinetics in Preclinical Studies

Plasma efavirenz concentrations achieved at maximally tolerated doses in rats were lower than those achieved in humans given efavirenz (in rats given 250 mg/kg bid of efavirenz the AUC was 38 μM•h in males and 84 μM•h in females). This was due, in part, to the autoinduction caused by efavirenz in rats. The resulting plasma half-life of efavirenz in rats is ≈0.8 to 1.9 hours, compared to a half-life of >40 hours in humans. Due to the low plasma efavirenz concentrations attained in rats, rats were a poor model in which to assess the toxicity of the parent drug. However, plasma concentrations of the primary efavirenz metabolite (the 8-OH--glucuronide conjugate) were 50- to 75- fold higher in rats given 250 mg/kg bid than in humans given therapeutic doses of efavirenz (the 8-OH-glucuronide conjugate was present at millimolar concentrations in the plasma of rats).

Chronic toxicity studies were conducted in cynomolgus monkeys in which the plasma efavirenz AUC values were higher than those attained in humans. AUC values achieved in cynomolgus monkeys given 45 mg/kg bid and 75 mg/kg bid during subchronic and chronic studies were ≈1.5- and 5-fold higher, respectively, than those achieved in humans given 600 mg/day (AUC values of 283 μM•h and 907 μM(h, respectively). In addition, the metabolic disposition of efavirenz in cynomolgus monkeys is similar to that in humans, although efavirenz is more extensively metabolized in cynomolgus monkeys than in humans.

Long-term Toxicity

The toxicity and toxicokinetics of efavirenz were evaluated in rats (duration of study ≤6 months), in rhesus monkeys (duration of study 1 month) and in cynomolgus monkeys (duration of study ≤1 year). In addition a 5 week oral toxicity study was conducted in newborn rhesus monkeys. From the subacute/chronic toxicological studies the following adverse effects have been noted following treatment with efavirenz.

Nephrotoxicity

The most prominent toxicologic finding in rats given efavirenz was nephrotoxicity. Rats treated with ≥250 mg/kg bid efavirenz in the 3-month oral toxicity study showed mild to moderate renal cortical epithelial cell necrosis, associated with intraluminal casts, proteinaceous debris, and tubular dilatation. In addition, late stage renal changes (occasionally leading to renal failure) occurred secondary to tubular obstruction and were characterized by cystic tubular dilatation and degeneration. Treatment of rats with doses ≥500 mg/kg bid occasionally resulted in death due to acute tubular necrosis. Renal lesions elicited by 1 month of dosing with 250 mg/kg bid of efavirenz were shown to be fully reversible following 1-month recovery period. The incidence of and severity of renal lesions was greater in male than female rats given equivalent efavirenz doses. The no effect dose for renal toxicity after ≥3 months of dosing was 100 mg/kg bid in female rats and 30 mg/kg bid in male rats.

Nephrotoxicity did not occur in cynomolgus monkeys given 75 mg/kg bid (AUC=907 μM(h) for 3 months to 1 year or in rhesus monkeys given 100 mg/kg/day for 1 month (AUC=212 μM(h). Average plasma efavirenz concentrations in monkeys in these studies exceeded those in rats given nephrotoxic doses of efavirenz.

Special toxicity studies implicated the formation of an efavirenz glutathione conjugate in the nephrotoxicity caused by efavirenz in rats. In these studies, interventions to decrease the formation and/or the catabolic products of glutathione conjugates resulted in decreased efavirenz-induced nephrotoxicity. Glutathione conjugates of efavirenz are not found in cynomolgus monkeys or in humans given efavirenz. Therefore, the nephrotoxicity elicited by efavirenz in rats is considered to be species specific.

Changes in the Biliary System

a) Biliary Fibrosis in Rats: An increased incidence of biliary fibrosis occurred in the liver of rats after oral gavage or dietary administration of doses ≥500 mg/kg/day. The severity of the change was minimal to mild, and was sparsely distributed involving relatively few isolated bile ducts. In rats given efavirenz in the diet for 3 months the lesions were sometimes accompanied by multifocal biliary hyperplasia (a possible consequence of increased biliary pressure in the drainage areas where fibrosis had occurred). Biliary lesions were not observed in rats given 100 mg/kg bid by oral gavage for 6 months or 100 mg/kg/day in the diet for 3 months.

b) Biliary Hyperplasia in Cynomolgus Monkeys: Minimal biliary hyperplasia (increase in the number of small caliber bile ducts) was observed in the liver of two of four male and two of four female monkeys in the high dose (75 mg/kg bid; AUC=907 μM(h) cynomolgus monkeys given efavirenz for 1 year. (Biliary hyperplasia was not seen in monkeys given this dose for 6 months or less.) There was no serum biochemical or histologic evidence of cholestasis and the change was not accompanied by fibrosis or histologic evidence of adjacent hepatocellular injury. In monkeys given the dose of 75 mg/kg bid, the mean plasma efavirenz AUC was approximately 5-fold greater than the AUC in humans given 600 mg/day of efavirenz (AUC=186 μM(h). The no effect level

for biliary hyperplasia (45 mg/kg bid for ≤1 year efavirenz (AUC=283 μM(h) was approximately 1.5-fold greater than in humans given 600 mg/day of efavirenz.

In a subsequent 2 year study total daily doses of ≥ 60 mg/kg/day resulted in minimal to moderate biliary hyperplasia in almost all of the animals. Plasma efavirenz exposure levels (120 mg/kg/day, AUC 1871 μM(h at 99 weeks) were higher in this study than in the 1 year study (see table 17).

Table 17

	Total Daily Dose	C_{max} range	AUC range
1 year study (T95-10-4)	150 mg/kg/day	32 - 72 μM	489 - 1262 μM.h
2 year study (T97-11-1)	150 mg/kg/day	42 - 159 μM	745 - 3173 μM.h

The biliary hyperplasia was not associated with any fibrotic or degenerative changes. The cause of biliary hyperplasia in cynomolgus monkeys following treatment with efavirenz remains unknown.

Minimal Thyroid Follicular Cell Hypertrophy

Minimal thyroid follicular hypertrophy was observed in cynomolgus monkeys given ≥45 mg/kg bid (AUC=283 μM(h) for 1 year but not in monkeys given 15 mg/kg bid (AUC=65 μM(h) for 1 year, or 100 mg/kg bid of efavirenz for ≤6 months or in rats. In a 2-year study in cynomolgus monkeys minimal-to-slight hypertrophy of thyroid follicular cells, was observed in the thyroid lobes of 1/11, 4/10, 8/10, and 1/5 monkeys given 0, 60, 150, or 150/80 mg/kg/day of DMP 266, respectively. In this study, thyroid follicular cell hypertrophy was not observed at the end of the 26-week recovery period. An increased clearance of 125l-thyroxine and elevations in serum thyroid stimulating hormone (TSH) were observed in cynomolgus monkeys given 75 mg/kg bid of efavirenz for 1 month. The thyroid follicular cell hypertrophy may be due to the induction of UDP-glucuronyl tranferase in this species (a rate limiting Phase II enzyme involved in the clearance of thyroxine).

ALT Elevations

Slight increases in serum ALT but not AST activity were observed in individual cynomolgus monkeys given ≥45 mg/kg bid (AUC ≥ 283 μM(h). The greatest individual ALT elevation was approximately 3-fold above the highest concurrent control, with the majority of the ALT elevations being mild (no more than approximately 1.5-fold above the highest concurrent control value). There was no evidence of hepatocellular injury after a year of dosing. No drug-related elevations of ALT were noted in rats or rhesus monkeys treated with efavirenz.

APTT and PT Prolongations

Slight increases in prothrombin time (PT) and activated partial thromboplastin time (APTT) were observed in some male rats given ≥50 mg/kg bid for 6 months. These prolongations were not associated with any gross or microscopic evidence of bleeding. No drug-related changes were found in the PT and APTT of female rats, nor were any prolongations observed in PT or APTT

of male or female rats in studies of ≤3 months duration. The cause of these prolongations in male rats is unknown.

In cynomolgus monkeys, slightly prolonged APTT (up to approximately 10 seconds above the upper limit of the reference range) were observed in some monkeys given 45 mg/kg bid (AUC=283 μM(h) or 75 mg/kg bid (AUC=907 μM(h) of efavirenz for > 6 months. The incidence and magnitude of the APTT prolongations increased with dose and the prolongations remained relatively constant over the course of the studies. Further investigation revealed a slight decrease in the activities of Factor XII in affected monkeys, and a slight decrease in the activity of Factor XI in the monkeys with the longest APTT. The decreased factor activity was not attributed to the presence of drug-induced inhibitor. Apart from decreased coagulation factor activities, no alteration in coagulation parameters, fibrinogen concentration, prothrombin time, or platelet count were noted. There was no evidence of gross or microscopic bleeding upon postmortem examination. The cause of decreased activities of Factor XII and/or XI is unknown.

Mutagenicity

Efavirenz was negative in a battery of in vitro and in vivo genotoxicity assays. This included assays in four in vitro assay systems: 1) bacterial mutation assays in Salmonella typhimurium and Escherichia coli, 2) a Chinese hamster ovary (CHO) cell/hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) forward mutation assays, 3) a chromosome aberration assay in human peripheral lymphocytes, and 4) a chromosome aberration assay in CHO cells, and in one in vivo system (mouse micronucleus assay). All assays were conducted employing maximally soluble or minimally toxic doses/concentrations of efavirenz.

Reproduction and Teratology

Malformations were observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in an ongoing developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (post-coital days 20-150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day. Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus.

No malformations were observed in fetuses from efavirenz-treated rats; however an increase in fetal resorptions and a slight increase in pup mortality was observed in rats at doses that produced peak plasma concentrations and AUC values in pregnant female rats similar to or lower than those achieved in humans at the recommended clinical dose. Efavirenz was not teratogenic or embryotoxic when given to pregnant rabbits.

<u>Peri/Postnatal Toxicity</u>

A 5-8% decrease in mean rat pup weights versus control mean rat pup weights, and a slight increase in rat pup mortality was observed at doses of 50 and 100 mg/kg bid in a study in which efavirenz was given to pregnant rats during gestation and through lactation until weaning (the 100 mg/kg bid dose produced peak plasma concentrations and AUC values in pregnant female rats similar to or lower than those achieved in humans at the recommended clinical dose). No

efavirenz-related effects were observed on the fertility, mating behavior, sexual maturation, learning, or behavior of the F1 generation derived from female rats given 100 mg/kg bid.

Maternal/Fetal Efavirenz Exposure

Fetal exposure to efavirenz was documented in pregnant rats, rabbits and cynomolgus monkeys. Maternal and fetal blood concentrations were equivalent in pregnant rabbits and cynomolgus monkeys and fetal blood concentrations were approximately 25% to 49% lower than the corresponding maternal concentrations in pregnant rats. Results of these studies indicated that efavirenz crossed the placenta in all species tested.

Efavirenz Concentration in Milk

The excretion of efavirenz into rat milk was demonstrated. Efavirenz milk concentrations in rats were approximately 8-fold higher than corresponding maternal efavirenz plasma concentrations.

Male/Female Fertility Assessment

No efavirenz-related effects were observed on the fertility or reproductive performance of female rats given 100 mg/kg bid, or on the reproductive performance or sperm motility and morphology of male rats given 200 mg/kg bid.

Assessment of Toxicity in Infant and Neonatal Non-Human Primates

In a five-week oral infant rhesus toxicity study, (dosing initiated on Day 2 of life at 30 and 45 mg/kg bid), infant rhesus monkeys given 30 mg/kg bid exhibited a slight, transitory decrease in body weight gain in females and slight decreases in food intake in females. Doses of 45 mg/kg bid produced adverse clinical signs in infant rhesus monkeys (vomiting, lethargy, dehydration, poor appetite, and/or weakness) and slight decreases in the average amount of body weight gain. No efavirenz-related hematology, serum biochemical, or histologic changes occurred at either dose.

Carcinogenesis

In a 2-year carcinogenicity study, mice were given daily oral dosages of 25, 75, 150 or 300 mg/kg/day of efavirenz. Because efavirenz is rapidly cleared in mice, plasma drug exposure (as measured by AUC) at dosages ≤150 mg/kg/day was lower than that in humans given 600 mg/day of efavirenz. In mice given 300 mg/kg/day of efavirenz, plasma drug exposure (AUC) was approximately 1.7-fold the AUC in humans given 600 mg/day of efavirenz. In female mice, a statistically significant, dose-related increase in the incidence of hepatic tumors occurred at dosages ≥75 mg/kg/day and a statistically significant, non dose-related increase in pulmonary tumors occurred at dosages ≥25 mg/kg/day of efavirenz. Efavirenz did not increase the incidence of any tumor type in male mice. Given the lack of genotoxic activity of efavirenz, the relevance to humans of hepatocellular tumors in efavirenz-treated mice is not known.

In a 2-year carcinogenicity study, rats were given daily oral dosages of 25, 50 or 100 mg/kg/day of efavirenz. Plasma drug exposures (as measured by AUC) in rats given all dosages of efavirenz were substantially below those achieved in humans given 600 mg/day of efavirenz, and therefore may not reflect the carcinogenic potential of efavirenz in humans. The low plasma drug exposures attained in rats are a consequence of the extremely rapid metabolic clearance of efavirenz in this species. However, virtually all of the efavirenz metabolites formed in rats are also formed in humans and the levels of these metabolites attained in the rat carcinogenicity study were likely substantially higher than those achieved in humans. Therefore, the results of this carcinogenicity study do provide meaningful information on the potential carcinogenicity of these efavirenz metabolites even at relatively low multiples of the parent drug exposure. Efavirenz did not increase the incidence of any tumor type in rats.

Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. In studies in which rats were administered efavirenz at doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above background were observed. The systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in human receiving the 600 mg/day dose. The exposure in rats was lower than that in humans.

The findings from the completed efavirenz mouse carcinogenicity study may not represent a significant risk to patients based upon the following: An increase in the incidence of hepatic tumors in efavirenz-treated mice was not unexpected as efavirenz is known to induce hepatic drug-metabolizing enzyme activity and enzyme inducers are known to increase the incidence of hepatic tumors in rodents, but not in humans. While the cause of the increased incidence of pulmonary tumors is not known, this finding also may not constitute a significant risk for patients given efavirenz because: (1) efavirenz is not genotoxic, (2) the strain of mice used in these studies is documented to have a high spontaneous background incidence of this tumor type, and (3) a decrease in the incidence of pulmonary tumors was observed in efavirenz-treated male mice. In male mice, plasma efavirenz concentrations were equal to or greater than in female mice.

REFERENCES

1. Bristol-Myers Squibb Canada, SUSTIVA® Product Monograph, Control Number 230875, December 12, 2019.

PART III: CONSUMER INFORMATION

[Pr] Mylan-Efavirenz
(efavirenz tablets)
600 mg

This leaflet is Part III of a three-part "Product Monograph" published when Mylan-Efavirenz was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Mylan-Efavirenz. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What is Mylan-Efavirenz?
- Mylan-Efavirenz is the brand name for the active ingredient efavirenz.

- Mylan-Efavirenz belongs to a class of anti-HIV medicines known as "non-nucleoside reverse transcriptase inhibitors" (NNRTIs or non-nukes).

What the medication is used for:
- Your doctor has prescribed Mylan-Efavirenz for you because you have been infected with HIV. Mylan-Efavirenz must always be taken in combination with other anti-HIV medicines (frequently referred to as "combination therapy").
- When taken with other anti-HIV medicines, efavirenz has been shown to reduce viral load and increase the number of CD4 cells (a type of immune cell in blood). Efavirenz may not have these effects in every patient.

Does Mylan-Efavirenz cure HIV or AIDS?
- Mylan-Efavirenz is not a cure for HIV nor Acquired Immunodeficiency Syndrome (AIDS). People taking Mylan-Efavirenz may still develop infections or other illnesses associated with HIV.
- It is very important that you remain under the constant care of your doctor while taking Mylan-Efavirenz.

Does Mylan-Efavirenz reduce the risk of passing HIV to others?
- Mylan-Efavirenz has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination. It is important to continue to practice safe sex and not use or share dirty needles.

What it does:
- Mylan-Efavirenz fights Human Immunodeficiency Virus (HIV) infection by reducing the amount of virus in the blood (called "viral load").

When it should not be used:
- Do not take Mylan-Efavirenz if you know you are allergic to any of the ingredients in the Mylan-Efavirenz tablets (See **What the nonmedicinal ingredients are**).
- Mylan-Efavirenz should not be taken with some other medicines that are listed in this pamphlet (see the section entitled "**Drugs that may interact with Mylan-Efavirenz**").

What the medicinal ingredient is:
Efavirenz

What the nonmedicinal ingredients are:
- Mylan-Efavirenz tablets also contain the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, sodium lauryl sulfate, hydroxypropyl cellulose, lactose monohydrate, and magnesium stearate. The film coating contains hypromellose, iron oxide red, iron oxide yellow, polyethylene glycol and titanium dioxide.

What dosage forms it comes in:
Each Mylan-Efavirenz tablet contains 600 mg of efavirenz.

WARNINGS AND PRECAUTIONS

BEFORE TAKING Mylan-Efavirenz
What should I tell my doctor before I start Mylan-Efavirenz?
- Inform your doctor about any past or present medical problems, including liver disease, hepatitis, allergies, severe kidney failure, seizures or mental illness.
- Inform your doctor if you have ever had a previous life-threatening skin reaction (e.g. Stevens-Johnson syndrome).
- Inform your doctor about any medications (prescription and nonprescription), herbal products, vitamins, nutritional supplements that you are currently taking or are planning to take.
- Also inform your doctor about any recreational (street, illicit) drugs that you are currently taking or are planning to take. The effect of combining recreational (street, illicit) drugs or alcohol with efavirenz has not been studied. Because they may interact with each other, speak with your doctor or other healthcare provider before you combine these drugs.
- Inform your doctor if you have or have had a heart rhythm disorder such as an irregular heartbeat, prolongation of the QT interval or any risk factors for Torsade de Pointes (dangerous fluttering of the heart).

What should I consider concerning contraception, pregnancy, or breast-feeding?
- Tell your doctor if you are pregnant or planning to become pregnant. Birth defects have been reported in the offsprings of animals and women treated with efavirenz during pregnancy. It is not known whether efavirenz caused these defects. Women should not become pregnant while taking Mylan-Efavirenz and for 12 weeks after stopping it. If you are pregnant, you should take Mylan-Efavirenz only if you and your doctor decide that the possible benefit to you is greater than the possible risk to your foetus. If you take Mylan-Efavirenz while you are pregnant, talk to your doctor about how you can be included in the antiretroviral pregnancy registry.

- Tell your doctor if you are breastfeeding or planning to breastfeed. It is currently recommended that HIV- infected women should not breastfeed. Discuss this with your doctor.
- A reliable form of barrier contraception must always be used even if you or your partner are using other methods of contraception such as the pill or other hormonal therapy (e.g., implants, injections). Mylan-Efavirenz may remain in your blood for a time after therapy is stopped. Therefore, you should continue use of a reliable form of contraception for 12 weeks after stopping treatment with Mylan-Efavirenz.

Can children take Mylan-Efavirenz?

- Efavirenz has not been studied in children below 3 years of age.

Do not drive or operate machinery until you have determined your response to Mylan-Efavirenz, as this may make you sleepy or dizzy.

Mylan-Efavirenz can cause abnormal blood test results. Your doctor may perform blood tests and will interpret the results.

To find out how to take Mylan-Efavirenz please read carefully the following section **"WHILE TAKING Mylan-Efavirenz".**

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Mylan-Efavirenz
Mylan-Efavirenz may affect the dosing of other medications including ones for treating HIV infection. For this reason it is very important to:

- Let all healthcare providers know that you are taking Mylan-Efavirenz.
- Inform your doctor and pharmacist about all medications that you are currently taking including those obtained over-the-counter without a prescription and complementary medications (vitamins, nutritional supplements, etc.) and herbal products, particularly St. John's Wort.
- Consult your doctor or pharmacist before you start any new medication.
- Consult your doctor or pharmacist before you stop any medications that you are currently taking.

Bring all your medications when you see your doctor. Or make a list of their names, how much you take, and how often you take them. This will give your doctor a complete picture of the medications you are taking. Then he or she can decide the best approach for your situation.

You must not take the following medications if you are taking Mylan-Efavirenz. Taking these medications with Mylan-Efavirenz could create the potential for serious and/or life-threatening side effects:

CISAPRIDE*[z]
MIDAZOLAM
TRIAZOLAM (e.g, HALCION*)
ERGOT MEDICATIONS (e.g, CAFERGOT*)
PIMOZIDE (e.g, ORAP*)
ZEPATIER
ST. JOHN'S WORT (*Hypericum perfo*ratum)

*[z] CISAPRIDE is not marketed in Canada

You must not take products containing St. John's wort (*Hypericum perforatum*) with Mylan-Efavirenz as this may stop Mylan-Efavirenz from working properly and may lead to resistance to Mylan-Efavirenz or resistance to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

The following drugs may interact with Mylan-Efavirenz and your doctor will determine whether they can be used or not or may make dosage changes for Mylan-Efavirenz or the other product, or substitute other products, as indicated below:

- Mylan-Efavirenz may be taken with many of the medications commonly used in people with HIV infection. These include the protease inhibitors, such as nelfinavir (Viracept*) and indinavir (Crixivan*), and nucleoside analogue reverse transcriptase inhibitors (NRTIs).
- **Use of Mylan-Efavirenz with saquinavir (Invirase*) is not recommended if you are taking saquinavir as your only protease inhibitor.**
- **VORICONAZOLE (VFEND***) should not be taken at standard doses with Mylan-Efavirenz since it may lose its effect or increase the chance of side effects from efavirenz. Some doses of voriconazole can be taken at the same time as a lower dose of efavirenz, but your doctor will decide if this is appropriate.
- Tegretol* (carbamazepine), Sporanox* (itraconazole), Posanol* (posaconazole) and REYATAZ (atazanavir sulfate), if this is not the first time you are receiving treatment for your HIV infection, may need to be replaced with another medicine when taken with efavirenz.
- Efavirenz reduces the blood levels of clarithromycin (Biaxin*) and is associated with a higher incidence of rash; your doctor may consider giving you an alternative antibiotic.
- If you are taking Mylan-Efavirenz and REYATAZ (atazanavir sulfate), you should also be taking Norvir* (ritonavir).
- Antimalarials such as atovaquone/proguanil, when taken with Mylan-Efavirenz, may reduce the amount of atovaquone/proguanil in your blood which may reduce the anti-malarial activity of these medicines. Atovaquone/proguanil should not be taken with Mylan-Efavirenz; your doctor should consider alternatives to these antimalarial medicines.
- Drugs that may interact with efavirenz to affect the electrical activity of your heart which include but may not be limited to macrolide antibiotics (such as clarithromycin) and antimalarials (artemether/lumefantrine).
- Use of EPCLUSA (sofosbuvir/velpatasvir), VOSEVI (sofosbuvir/velpatasvir/voxilaprevir), and MAVIRET (glecaprevir/pibrentasvir) is not recommended when taking Mylan-Efavirenz.
- Mylan-Efavirenz may interact with etonogestrel contraceptive implants. This means your implant might not work and you could get pregnant. You should use a barrier

birth control method like a condom. Talk to your healthcare professional for advice on additional birth control methods.

The following medicine should not be taken with Mylan-Efavirenz since it contains efavirenz, the active ingredient in Mylan-Efavirenz:

- ATRIPLA (efavirenz, emtricitabine, tenofovir disoproxil fumarate) unless your doctor decides a dose adjustment is needed (e.g, with rifampin).

- Your doctor may need to adjust the dose of either Mylan-Efavirenz or the following medications when taken with Mylan-Efavirenz:
  - Crixivan* (indinavir)
  - Methadone
  - Zoloft* (sertraline)
  - Wellbutrin SR, Wellbutrin XL or Zyban (buproprion)
  - Kaletra* (lopinavir/ritonavir) Lopinavir and ritonavir combination should not be taken once daily with efavirenz. Your doctor may suggest an alternate dosing regimen.
  - Celsentri* (maraviroc)
  - Mycobutin* (rifabutin)
  - The cholesterol-lowering medicines Lipitor* (atorvastatin), Pravachol* (pravastatin), and Zocor* (simvastatin)
  - Rifadin* (rifampin) or the rifampin-containing medicines Rofact* and Rifater*
  - Calcium channel blockers such as Cardizem* or Tiazac* (diltiazem), Covera HS, Isoptin SR or Tarka (verapamil), and others.
  - Immunosuppressants such as Neoral* (cyclosporin), Advagraf* or Prograf* (tacrolimus), Rapamune* or Torisel* (sirolimus)
  - Hepatitis C antiviral agents
  - Antimalarials such as Coartem*[#] and Riamet*[#] (artemether/lumefantrine)

Not marketed in Canada

- The effect of combining alcohol or recreational (street, illicit) drugs with Mylan-Efavirenz has not been studied. Because they may interact with each other, speak with your doctor or other healthcare provider before you combine these drugs.

PROPER USE OF THIS MEDICATION

WHILE TAKING Mylan-Efavirenz

Usual Dose

- The dose of Mylan-Efavirenz for adults and children weighing more than 40 kg (88 lbs) is 600 mg once-a- day (one 600 mg tablet).
- The dose for children weighing 40 kg or less is determined by the weight of the child and is taken once daily.
- You should take Mylan-Efavirenz on an empty stomach, preferably at bedtime. Taking Mylan-Efavirenz with food increases the level of efavirenz in the blood and may increase the possibility of side effects.
- Your doctor or pharmacist will give you instructions for proper dosage.

What should I remember to do or avoid while taking Mylan-Efavirenz?

- Swallow Mylan-Efavirenz with water.
- Do not chew the tablets.
- Taking Mylan-Efavirenz at bedtime may improve the tolerability of the nervous system side effects.
- It is important to take Mylan-Efavirenz as your doctor prescribes. Do not change the dose on your own.
- Mylan-Efavirenz should not be used alone to treat HIV. Mylan-Efavirenz should always be taken with other anti-HIV medications in order to prevent the virus from becoming resistant to your drug treatment.
- You should not stop taking Mylan-Efavirenz without first consulting with your doctor.
- If you are unsure of what to do or need help in planning the best times to take your medications, ask your doctor or other healthcare provider.
- If you think it would be useful, ask a friend or family member to remind you to take your medications.
- When your Mylan-Efavirenz supply starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if Mylan-Efavirenz is stopped for even a short time. The virus may then become harder to treat.
- Remember, Mylan-Efavirenz has been prescribed just for you. Never give your medications to others to try.
- Do not use your current supply of Mylan-Efavirenz after the end of the month and year shown by the "expiry date" on the bottle.

Overdose:

In case of drug overdosage, contact a healthcare practitioner (e.g. doctor) hospital emergency department or regional poison control centre, even if there are no symptoms.

Missed Dose:

- If you forget to take Mylan-Efavirenz, **do not double your next dose**. Take the missed dose as soon as possible, and then carry on with your regular dosing schedule.
- Try not to miss a dose. With anti-HIV medications, missing doses or not taking them properly may allow the amount of HIV in your body to increase. HIV may then become resistant. This means that the virus changes or mutates causing a medication to lose its effect.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- Mylan-Efavirenz, like all medications, affects different people in different ways. Any medication may have unintended or unwanted effects, so-called side effects. Some people may develop side effects, others may not.
- The most notable side effects of efavirenz are rash and nervous system symptoms that include dizziness, insomnia (difficulty falling asleep), drowsiness, reduced ability to concentrate, and abnormal dreaming. These side effects are generally mild to moderate and tend to disappear after you

have taken efavirenz for a few weeks. Decreasing the dose does not seem to help and is not recommended.
- Some of these side effects such as dizziness will likely be less noticeable if you take Mylan-Efavirenz before going to bed. Be sure to tell your doctor if any of these side effects continue or if they bother you.
- A small number of patients have had severe depression, strange thoughts, or angry behavior. Some patients have had thoughts of suicide and a few patients have actually committed suicide. These problems tend to occur more often in patients with a history of mental illness. You should contact your doctor immediately if you think you are having these symptoms, so your doctor can decide whether you should continue to take efavirenz.
- Dizziness, trouble concentrating, and drowsiness have been reported with efavirenz. If you notice any of these symptoms you should avoid potentially hazardous tasks such as driving or operating machinery.
- You should consult your doctor if you have a rash since some rashes may be serious. However, most cases of rash disappear without any change in your treatment.
- Rash seems to be more common in children than in adults treated with efavirenz.
- Some patients taking efavirenz have experienced serious liver problems including liver failure resulting in transplantation or death. Most of these serious side effects occurred in patients with a chronic liver disease such as a hepatitis infection, but there have also been a few reports in patients without any existing liver disease.
- Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Autoimmune disease (when the immune system attacks healthy body tissue) may also occur after you start taking medicines for HIV infection. Examples of this include the following conditions: Grave's disease, Guillain-Barre syndrome, polymyositis or autoimmune hepatitis]. Autoimmune disorders may occur many months after the start of treatment. Look for any symptoms such as:
    - fever, redness, rash or swelling
    - fatigue
    - joint or muscle pain
    - numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body
    - palpitations (chest pain) or rapid heart rate
    - bulging eyes, light sensitivity, or vision changes
    - yellowing of the skin
    - difficulty talking, chewing, or
    - swallowing

If you notice any of these symptoms, tell your doctor immediately.

Other side effects
- Other common side effects that have been reported include tiredness, nausea, diarrhea and headache. These may be from efavirenz or from other medications that you are taking.
- Tell your doctor or other healthcare provider if you notice these or any other side effects not mentioned in the pamphlet that continue or if they bother you.

Remember do not stop taking Mylan-Efavirenz without speaking to your doctor first. He or she may be able to help you manage these side effects without stopping your anti-HIV medications.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Effect/Symptom	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
		Only if severe	**In all cases**	
Common	**Serious psychiatric events** **Symptoms:** • Severe depression • Thoughts of suicide • Strange thoughts • Angry behavior • Catatonia (unable to move or speak normally)		✓	
Uncommon	**Severe skin rash** **Symptoms:** • Blisters or peeling of the skin • Blisters or peeling of the mouth, lips and throat • Fever and general ill feeling			✓
Rare	**Liver failure** **Symptoms:** • Jaundice (skin or the white part of eyes turn yellow) • Urine turns dark • Bowel movements (stools) turn light in colour • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain		✓	

This is not a complete list of side effects. If you have any unexpected effects while taking Mylan-Efavirenz, contact your doctor or pharmacist.

HOW TO STORE IT

Mylan-Efavirenz should be stored between 15°C and 30°C.

As with all medications, Mylan-Efavirenz should be kept out of the reach and sight of children.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Mylan-Efavirenz:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) or by calling 1-844-596-9526

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