HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUSTIVA safely and effectively. See full prescribing information for SUSTIVA.

SUSTIVA® (efavirenz) capsules and tablets

Initial U.S. Approval: 1998

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

Warnings and Precautions, Reproductive Risk Potential (5.6) 3/2009

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

SUSTIVA is a non-nucleoside reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 infection. (1)

-------------------------DOSE AND ADMINISTRATION-------------------------

• SUSTIVA should be taken orally once daily on an empty stomach, preferably at bedtime. (2)

• Recommended adult dose: 600 mg. (2.1)

• With voriconazole, increase voriconazole maintenance dose to 400 mg every 12 hours and decrease SUSTIVA dose to 300 mg once daily using the capsule formulation. (2.1)

Pediatric Patients at Least 3 Years and at Least 10 kg (2.2)

<table>
<thead>
<tr>
<th>kg</th>
<th>mg</th>
<th>kg</th>
<th>mg</th>
<th>kg</th>
<th>mg</th>
<th>kg</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>22</td>
<td>15</td>
<td>25</td>
<td>15</td>
<td>33</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>20</td>
<td>44</td>
<td>30</td>
<td>55</td>
<td>30</td>
<td>62</td>
<td>30</td>
<td>62</td>
</tr>
</tbody>
</table>

-------------------------DOSE FORMS AND STRENGTHS-------------------------

• Capsules: 200 mg and 50 mg. (3)

• Tablets: 600 mg. (3)

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

• SUSTIVA is contraindicated in patients with previously demonstrated hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4.1)

• For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). (4.2)

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

• Do not use as a single agent or add on as a sole agent to a failing regimen. Consider potential for cross resistance when choosing other agents. (5.2)

• Not recommended with ATRIPLA, which contains efavirenz, emtricitabine, and tenofovir disoproxil fumarate. (5.3)

• Serious psychiatric symptoms: Immediate medical evaluation is recommended for serious psychiatric symptoms such as severe depression or suicidal ideation. (5.4, 17.5)

• Nervous system symptoms (NSS): NSS are frequent, usually begin 1-2 days after initiating therapy and resolve in 2-4 weeks. Dosing at bedtime may improve tolerability. NSS are not predictive of onset of psychiatric symptoms. (5.5, 6.1, 17.4)

• Pregnancy: Fetal harm can occur when administered to a pregnant woman during the first trimester. Women should be apprised of the potential harm to the fetus. (5.6, 17.7)

• Hepatotoxicity: Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B and C, or marked transaminase elevations. (5.8, 6.6)

• Rash: Rash usually begins within 1-2 weeks after initiating therapy and resolves within 4 weeks. Discontinue if severe rash develops. (5.9)

• Convulsions: Use caution in patients with a history of seizures. (5.10)

• Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.11)

• Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy. (5.12, 17.8)

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

Most common adverse reactions (≥5%, moderate-severe) are rash, dizziness, nausea, headache, fatigue, insomnia, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

Coadministration of efavirenz can alter the concentrations of other drugs and other drugs may alter the concentrations of efavirenz. The potential for drug-drug interactions must be considered before and during therapy. (4.2, 7.1, 12.3)

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

• Pregnancy: Women should avoid pregnancy during SUSTIVA (efavirenz) therapy and for 12 weeks after discontinuation. (5.6)

• Nursing mothers: Women infected with HIV should be instructed not to breast-feed. (8.3)

• Hepatitis B or C coinfection or therapy with medications associated with liver toxicity: Use caution in patients with hepatic impairment. (5.8, 6.1, 8.6)

• Pediatric patients: The incidence of rash was higher than in adults. (5.7, 6.1, 6.2, 8.4)

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

Revised: 09/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

1  INDICATIONS AND USAGE

2  DOSAGE AND ADMINISTRATION

2.1 Adults

2.2 Pediatric Patients

3  DOSE FORMS AND STRENGTHS

4  CONTRAINDICATIONS

4.1 Hypersensitivity

4.2 Contraindicated Drugs

5  WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

5.2 Resistance

5.3 Coadministration with Related Products

5.4 Psychiatric Symptoms

5.5 Nervous System Symptoms

5.6 Reproductive Risk Potential

5.7 Rash

5.8 Liver Enzymes

5.9 Convulsions

5.10 Lipid Elevations

5.11 Immune Reconstitution Syndrome

5.12 Fat Redistribution

6  ADVERSE REACTIONS

6.1 Clinical Trials Experience in Adults

6.2 Clinical Trial Experience in Pediatric Patients

6.3 Postmarketing Experience

7  DRUG INTERACTIONS

7.1 Drug-Drug Interactions

7.2 Cannabinoid Test Interaction

8  USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Capsules

16.2 Tablets

16.3 Storage

17 PATIENT COUNSELING INFORMATION

Revised: 09/2009

* Sections or subsections omitted from the full prescribing information are not listed
SUSTIVA® (efavirenz)

Full Prescribing Information

1 Indications and Usage

SUSTIVA (efavirenz) in combination with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. This indication is based on two clinical trials of at least one year duration that demonstrated prolonged suppression of HIV RNA [see Clinical Studies (14)].

2 Dosage and Administration

2.1 Adults

The recommended dosage of SUSTIVA (efavirenz) is 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs). It is recommended that SUSTIVA be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration of SUSTIVA with food may lead to an increase in frequency of adverse reactions [see Clinical Pharmacology (12.3)]. Dosing at bedtime may improve the tolerability of nervous system symptoms [see Warnings and Precautions (5.4), Adverse Reactions (6.1), and Patient Counseling Information (17.4)].

Concomitant Antiretroviral Therapy

SUSTIVA must be given in combination with other antiretroviral medications [see Indications and Usage (1), Warnings and Precautions (5.2), Drug Interactions (7.1), and Clinical Pharmacology (12.3)].

Dosage Adjustment

If SUSTIVA is coadministered with voriconazole, the voriconazole maintenance dose should be increased to 400 mg every 12 hours and the SUSTIVA dose should be decreased to 300 mg once daily using the capsule formulation (one 200-mg and two 50-mg capsules or six 50-mg capsules). SUSTIVA tablets should not be broken. See Drug Interactions (7.1, Table 7) and Clinical Pharmacology (12.3, Tables 8 and 9).

2.2 Pediatric Patients

It is recommended that SUSTIVA be taken on an empty stomach, preferably at bedtime. Table 1 describes the recommended dose of SUSTIVA for pediatric patients 3 years of age or older and weighing between 10 and 40 kg [see Use in Specific Populations (8.4)]. The recommended dosage of SUSTIVA for pediatric patients weighing greater than 40 kg is 600 mg once daily.

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>SUSTIVA Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>kg</td>
<td>lbs</td>
</tr>
<tr>
<td>10 to less than 15</td>
<td>22 to less than 33</td>
</tr>
<tr>
<td>15 to less than 20</td>
<td>33 to less than 44</td>
</tr>
<tr>
<td>20 to less than 25</td>
<td>44 to less than 55</td>
</tr>
<tr>
<td>25 to less than 32.5</td>
<td>55 to less than 71.5</td>
</tr>
<tr>
<td>32.5 to less than 40</td>
<td>71.5 to less than 88</td>
</tr>
<tr>
<td>at least 40</td>
<td>at least 88</td>
</tr>
</tbody>
</table>

3 Dosage Forms and Strengths

• Capsules

200-mg capsules are gold color, reverse printed with “SUSTIVA” on the body and imprinted “200” on the cap. 50-mg capsules are gold color and white, printed with “SUSTIVA” on the gold color cap and reverse printed “50 mg” on the white body.

• Tablets

600-mg tablets are yellow, capsule-shaped, film-coated tablets, with “SUSTIVA” printed on both sides.

4 Contraindications

4.1 Hypersensitivity

SUSTIVA is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.

4.2 Contraindicated Drugs

For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated with SUSTIVA are listed in Table 2.

<table>
<thead>
<tr>
<th>Drug Class: Drug Name</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimigraine: ergot derivatives (dihydropyrgotamine, ergonovine, ergotamine, methylergonovine)</td>
<td>Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.</td>
</tr>
<tr>
<td>Benzodiazepines: midazolam, triazolam</td>
<td>Potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.</td>
</tr>
<tr>
<td>Calcium channel blocker: bepridil</td>
<td>Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.</td>
</tr>
</tbody>
</table>

(Continued)

5 Warnings and Precautions

5.1 Drug Interactions

Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A. Likewise, efavirenz may alter plasma concentrations of drugs metabolized by CYP3A [see Contraindications (4.2) and Drug Interactions (7.1)].

5.2 Resistance

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

5.3 Coadministration with Related Products

Coadministration of SUSTIVA with ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) is not recommended, since efavirenz is one of its active ingredients.

5.4 Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with SUSTIVA. In controlled trials of 1008 patients treated with regimens containing SUSTIVA for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among patients who received SUSTIVA or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonsuicidal suicide attempts (0.5%), 0, aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study 006, treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the SUSTIVA and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both SUSTIVA-treated and control-treated patients. One percent of SUSTIVA-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior, although a causal relationship to the use of SUSTIVA cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of SUSTIVA, and if so, to determine whether the risks of continued therapy outweigh the benefits. See Adverse Reactions (6.1).

5.5 Nervous System Symptoms

Fifty-three percent (531/1008) of patients receiving SUSTIVA in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens [see Adverse Reactions (6.1, Table 4)]. These symptoms included, but were not limited to, dizziness (28.1% of the 1008 patients), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in 2.0% of patients, and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing SUSTIVA and from 3% to 5% in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms [see Warnings and Precautions (5.4)]. Dosing at bedtime may improve the tolerability of these nervous system symptoms [see Dosage and Administration (2)]. Analysis of long-term data from Study 006 (median follow-up 180 weeks, 102 weeks, and 76 weeks for patients treated with SUSTIVA + zidovudine + lamivudine, SUSTIVA + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among SUSTIVA-treated patients were generally similar to those in the indinavir-containing control arm.

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

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

Pregnancy Category D. Efavirenz may cause fetal harm when administered during the first trimester of pregnancy. Pregnancy should be avoided in women receiving SUSTIVA. Barrier contraception must always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of SUSTIVA is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of SUSTIVA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

There are no adequate and well-controlled studies in pregnant women. SUSTIVA 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 SUSTIVA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

As of July 2008, the Antiretroviral Pregnancy Registry has received prospective reports of 526 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures. Birth defects occurred in 13 of 407 live births (first-trimester exposure) and 2 of 37 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 defect associated with anophthalmia.

There have been five retrospective reports of findings consistent with neural tube defects, Including anophthalmia, in one fetus, microophthalmia was observed in preclinical studies of efavirenz. Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital 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 of SUSTIVA. Anencephaly and unilateral anophthalmia were observed in one fetus, microphthalmia was observed in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of SUSTIVA. Efavirenz produces no reproductive toxicity in male rodents, male cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital 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 of SUSTIVA. Anencephaly and unilateral anophthalmia were observed in one fetus, microphthalmia was observed in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of SUSTIVA.

5.7 Rash

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg SUSTIVA experienced new-onset skin rash compared with 17% (111/635) of patients treated in control groups. See Table 5:   Selected Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity in Adults. Rash was associated with pruritus, mild desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with SUSTIVA. The incidence of Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in patients treated with SUSTIVA in all studies and expanded access was 0.1%. Rash is usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 1.7% (17/1100). SUSTIVA can be reintroduced in patients continuing therapy because of rash. SUSTIVA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Rash was reported in 26 of 57 pediatric patients (46%) treated with SUSTIVA capsules (see Adverse Reactions (6.1, 6.2)). One pediatric patient had Grade 3 rash (confluent rash with fever), and two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 8 days. Prophylaxis with appropriate antihistamines before initiating therapy with SUSTIVA in pediatric patients should be considered.

5.8 Liver Enzymes

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continuing therapy with SUSTIVA needs to be weighed against the unknown risks of significant liver toxicity (see Adverse Reactions (6.1) and Use in Specific Populations (8.6)).

5.9 Conclusions

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

5.10 Lipid Elevations

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

5.11 Immune Reconstitution Syndrome

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

5.12 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

6 ADVERSE REACTIONS

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

- Psychiatric symptoms [see Warnings and Precautions (5.4)],
- Nervous system symptoms [see Warnings and Precautions (5.5)],
- Rash [see Warnings and Precautions (5.7)].

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

6.1 Clinical Trials Experience in Adults

Because clinical studies are conducted under widely varying conditions, the adverse reaction rates reported cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in clinical practice. Selected clinical adverse reactions of moderate or severe intensity observed in ≥2% of SUSTIVA-treated patients in two controlled clinical trials are presented in Table 3.

Table 3:   Selected Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Reported in ≥2% of SUSTIVA-Treated Patients in Studies 006 and ACTG 364

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Study 006 ZDV/LAM, NNRTI-, and Protease Inhibitor-Naive Patients</th>
<th>Study ACTG 364 NNRTI-experienced, NNRTI- and Protease Inhibitor-Naive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZDV/LAM</td>
<td>Indinavir</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Pain</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Central and Peripheral Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Headache</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Concentration impaired</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Includes adverse events at least possibly related to study drug or of unknown relationship to study drug for Study ACTG 364. SUSTIVA provided as 600 mg once daily.
* Median duration of treatment.
* Includes erythema multiforme, rash, rash exfoliative, rash folicular, rash maculopapular, rash pustular, rash purpuric, and urticaria for Study 006, and macules, papules, rash, erythema, redness, inflammation, allergic rash, urticaria, welts, hives, itch, and pruritus for ACTG 364.

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

Nervous System Symptoms
For 1008 patients treated with regimens containing SUSTIVA and 635 patients treated with a control regimen in controlled trials, Table 4 lists the frequency of symptoms of different degrees of severity and gives the discontinuation rates for one or more of the following nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization [see Warnings and Precautions (5.7)]. The frequencies of specific central and peripheral nervous system symptoms are provided in Table 3.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SUSTIVA®</th>
<th>SUSTIVA®, and Protease Inhibitor-Naive Patients</th>
<th>Study ACTG 364</th>
<th>NRTI-experienced, NNRTI- and Protease Inhibitor-Naive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study 006</td>
<td>(n=412)</td>
<td>Study ACTG 364</td>
<td>(n=64)</td>
</tr>
<tr>
<td></td>
<td>ZDV/LAM</td>
<td>Indinavir</td>
<td>ZDV/LAM</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>102 weeks</td>
<td>76 weeks</td>
<td>71.1 weeks</td>
<td>70.9 weeks</td>
</tr>
<tr>
<td>Skin &amp; Appendages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>&lt;1%</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Nervousness</td>
<td></td>
<td>2%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>5%</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td>2%</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Table 4: Percent of Patients with One or More Selected Nervous System Symptoma,b

<table>
<thead>
<tr>
<th>Percent of Patients with:</th>
<th>SUSTIVA 600 mg Once Daily (n=1008) %</th>
<th>Control Groups (n=635) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of any severity</td>
<td>52.7</td>
<td>24.6</td>
</tr>
<tr>
<td>Mild symptoms</td>
<td>33.3</td>
<td>15.6</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>17.4</td>
<td>7.7</td>
</tr>
<tr>
<td>Severe symptoms</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Treatment discontinuation as a result of symptoms</td>
<td>2.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

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

Rash
For 1008 adults and 57 pediatric patients treated with regimens containing SUSTIVA and 635 patients treated with a control regimen in controlled trials, the frequency of rash by NCI grade and the discontinuation rates as a result of rash in clinical studies are provided in Table 5 [see Warnings and Precautions (5.7)].

Table 5: Percent of Patients with Treatment-Emergent Rashab

<table>
<thead>
<tr>
<th>Percent of Patients with:</th>
<th>Description of Rash Gradea</th>
<th>SUSTIVA 600 mg Once Daily Adults (n=1008) %</th>
<th>SUSTIVA Pediatric Adults (n=57) %</th>
<th>Control Groups Adults (n=635) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash of any grade</td>
<td>—</td>
<td>26.3</td>
<td>45.6</td>
<td>17.5</td>
</tr>
<tr>
<td>Grade 1 rash</td>
<td>Erythema, pruritus</td>
<td>10.7</td>
<td>8.8</td>
<td>9.8</td>
</tr>
<tr>
<td>Grade 2 rash</td>
<td>Diffuse maculopapular rash, dry desquamation</td>
<td>14.7</td>
<td>31.6</td>
<td>7.4</td>
</tr>
<tr>
<td>Grade 3 rash</td>
<td>Vesiculosis, moist desquamation, ulceration</td>
<td>0.8</td>
<td>1.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Grade 4 rash</td>
<td>Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis</td>
<td>0.1</td>
<td>3.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Treatment discontinuation as a result of rash
— 1.7
— 8.8
— 0.3

Table 6: Selected Grade 3-4 Laboratory Abnormalities Reported in >2% of SUSTIVA-Treated Patients in two clinical trials are presented in Table 6.

SUSTIVA® (efavirenz)
Lipids
Increases from baseline in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving SUSTIVA. In patients treated with SUSTIVA + zidovudine + lamivudine, increases from baseline in nonfasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with SUSTIVA + indinavir, increases from baseline in nonfasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed. Nonfasting total cholesterol levels ≥240 mg/dL and ≥300 mg/dL were reported in 34% and 9%, respectively, of patients treated with SUSTIVA + zidovudine + lamivudine; 54% and 20%, respectively, of patients treated with SUSTIVA + indinavir; and 28% and 4%, respectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of SUSTIVA on triglycerides and LDL in this study were not well characterized since samples were taken from nonfasting patients. The clinical significance of these findings is unknown [see Warnings and Precautions (5.10)].

6.2 Clinical Trial Experience in Pediatric Patients
Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3 to 16 years who received SUSTIVA capsules, nevirapine, and one or more NRTIs in Study ACTG 382 [see Use In Specific Populations (8.4)] were rash (46%), diarrhea/loose stools (39%), fever (21%), cough (16%), dizziness/lightheadedness (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 (5.7) and Adverse Reactions (6.1, Table 5)].

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

Body as a Whole: allergic reactions, asthenia, redistribution/accumulation of body fat [see Warnings and Precautions (5.12)]

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

Endocrine/gynecomastia

Gastrointestinal: constipation, malabsorption

Cardiovascular: flushing, palpitations

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

Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia

Musculoskeletal: arthralgia, myalgia, myopathy

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

Respiratory: dyspnea

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

Special Senses: abnormal vision, tinnitus

7 DRUG INTERACTIONS
7.1 Drug-Drug Interactions
Efavirenz has been shown in vivo to induce CYP3A. Other compounds that are substrates of CYP3A may have decreased plasma concentrations when coadministered with SUSTIVA. In vitro studies have demonstrated that efavirenz inhibits CYP2C9, 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.

Drugs that induce CYP3A activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lower plasma concentrations. Drug interactions with SUSTIVA are summarized in Tables 2 and 7 (Continued) for pharmacokinetics data see Clinical Pharmacology (12.3, Tables 8 and 9). The tables include potentially significant interactions, but are not all inclusive.

Table 7: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitor:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir + calcium</td>
<td>↓ ampranavir</td>
<td>Fosamprenavir (unboosted); Appropriate doses of the combinations with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when SUSTIVA is administered concomitantly with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when SUSTIVA is administered concomitantly with fosamprenavir plus ritonavir twice daily.</td>
</tr>
<tr>
<td>Protease inhibitor:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>↓ atazanavir</td>
<td>Treatment-naive patients: When coadministered with SUSTIVA, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and SUSTIVA 600 mg (once daily on an empty stomach, preferably at bedtime). Treatment-experienced patients: Coadministration of SUSTIVA and atazanavir is not recommended.</td>
</tr>
<tr>
<td>Protease inhibitor:</td>
<td>↓ indinavir</td>
<td>The optimal dose of indinavir, when given in combination with SUSTIVA, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to SUSTIVA. When indinavir at an increased dose (1000 mg every 8 hours) was given with SUSTIVA (600 mg once daily), the indinavir AUC and Cmax were decreased on average by 33-46% and 39-57%, respectively, compared to when indinavir (600 mg every 8 hours) was given alone.</td>
</tr>
<tr>
<td>Protease inhibitor:</td>
<td>↓ lopinavir</td>
<td>Lopinavir/ritonavir tablets should not be administered once-daily in combination with SUSTIVA. In antiretroviral-naive patients, lopinavir/ritonavir tablets can be used twice daily in combination with SUSTIVA 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 SUSTIVA in treatment-experienced patients, where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). A dose increase of lopinavir/ritonavir oral solution to 533/133 mg (6.5 mL) twice daily taken with food is recommended when used in combination with SUSTIVA.</td>
</tr>
<tr>
<td>Protease inhibitor:</td>
<td>↓ saquinavir</td>
<td>Should not be used as sole protease inhibitor in combination with SUSTIVA.</td>
</tr>
<tr>
<td>Other agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>↑ or ↓ warfarin</td>
<td>Plasma concentrations and effects potentially increased or decreased by SUSTIVA.</td>
</tr>
<tr>
<td>Anticonvulsants:</td>
<td>↓ or ↓ anticonvulsant</td>
<td>There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↓ anticonvulsant</td>
<td>Potential reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.</td>
</tr>
<tr>
<td>Antidepressants:</td>
<td>↓ sertraline</td>
<td>Increases in sertraline dosage should be guided by clinical response.</td>
</tr>
<tr>
<td>Antifungals:</td>
<td>↓ voriconazole</td>
<td>SUSTIVA and voriconazole must not be coadministered at standard doses. Efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of SUSTIVA-associated side effects. When voriconazole is coadministered with SUSTIVA, voriconazole maintenance dose should be increased to 400 mg every 12 hours and SUSTIVA dose should be decreased to 300 mg once daily using the capsule formulation. SUSTIVA tablets should not be broken. [See Dosage and Administration (2.1) and Clinical Pharmacology (12.3, Tables 8 and 9).]</td>
</tr>
</tbody>
</table>

Note: Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
### Table 7: Established and Other Potentially Significant\(^a\) Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (Continued)

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other agents (Continued)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungal:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>↓</td>
<td>hydroxyitraconazole(^a)</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>↓</td>
<td>ketocazole</td>
</tr>
<tr>
<td>Anti-inflammatory:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>↓</td>
<td>clarithromycin(^a)</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>↓</td>
<td>rifabutin(^a)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>↓</td>
<td>efavirenz(^a)</td>
</tr>
<tr>
<td>Calcium channel blockers:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>↓</td>
<td>diltiazem(^a)</td>
</tr>
<tr>
<td>Calcium channel blocker (N)-monodesmethyl diltiazem</td>
<td>↓</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↓</td>
<td>atorvastatin(^a)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>↓</td>
<td>pravastatin(^a)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↓</td>
<td>simvastatin(^a)</td>
</tr>
<tr>
<td>Hormonal contraceptives:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Ethinyl estradiol/ (N)-orgestone</td>
<td>↓</td>
<td>active metabolites of (N)-orgestone(^a)</td>
</tr>
<tr>
<td>Implant Etonogestrel</td>
<td>↓</td>
<td>etonogestrel</td>
</tr>
<tr>
<td>Immunosuppressants: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A</td>
<td>↓</td>
<td>immunosuppressant</td>
</tr>
</tbody>
</table>

### Table 7: Established and Other Potentially Significant\(^a\) Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (Continued)

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Narcotic analgesic: Methadone</strong></td>
<td>↓</td>
<td>methadone(^a)</td>
</tr>
</tbody>
</table>

\(^a\) See Clinical Pharmacology (12.3, Tables 8 and 9) for magnitude of established interactions. \(^b\) This table is not all-inclusive.

### Other Drugs

Based on the results of drug interaction studies [see Clinical Pharmacology (12.3, Tables 8 and 9), no dosage adjustment is recommended when SUSTIVA (efavirenz) is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cefepime, ceftriaxone, clarithromycin, nifedipine, felodipine, propranolol, nadolol, verapamil, tamofoxen, disopyramide, furosamide, and zidovudine]. Specific drug interaction studies have not been performed with SUSTIVA 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.

### 7.2 Cannabinoid Test Interaction

Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving SUSTIVA when the Microgenics CEDIA DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry. Of the three assays analyzed [Microgenics CEDIA DAU Multi-Level THC assay, Cannabinoid Enzyme Immunoassay (Diagnostic Reagents, Inc), and AxSYM Cannabinoid Assay], only the Microgenics CEDIA DAU Multi-Level THC assay showed false-positive results. The other two assays provided true-negative results. The effects of SUSTIVA on cannabinoid screening tests other than these three are unknown. The manufacturers of cannabinoid assays should be contacted for additional information regarding the use of their assays with patients receiving efavirenz.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

Pregnancy Category D: See Warnings and Precautions (5.6).

#### 8.2 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid postnatal transmission of HIV. Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats. Because of the potential for HIV transmission and the potential for serious adverse effects in nursing infants, mothers should be instructed not to breast-feed if they are receiving SUSTIVA.

#### 8.3 Pediatric Use

ACTG 382 is an ongoing, open-label study in 57 NRTI-experienced pediatric patients to characterize the safety, pharmacokinetics, and antiviral activity of SUSTIVA in combination with nelfinavir (20-30 mg/kg three times daily) and NRTIs. Mean age was 8 years (range 3-16). SUSTIVA 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 Warnings and Precautions (5.7) and Adverse Reactions (6.1, Table 5: 6.2)].

The starting dose of SUSTIVA was 600 mg once daily adjusted to body size, based on weight, targeting AUC levels in the range of 190-380 μM*h [see Dosage and Administration (2.2)]. The pharmacokinetics of efavirenz in pediatric patients were similar to the pharmacokinetics in adults who received 600 mg daily doses of SUSTIVA. In 48 pediatric patients receiving the equivalent of a 600-mg dose of SUSTIVA, steady-state C\textsubscript{max} was 14.2 ± 5.8 μM (mean ± SD), steady-state C\textsubscript{min} was 5.6 ± 4.1 μM, and AUC was 218 ± 104 μM*h.

#### 8.4 Geriatric Use

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

#### 8.5 Hepatic Impairment

The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering SUSTIVA to these patients [see Warnings and Precautions (5.8)].
10 OVERDOSE
Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions. Treatment of overdose with SUSTIVA should consist of general supportive measures, including monitoring of vital signs and observation of the patient’s clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with SUSTIVA. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

11 DESCRIPTION
SUSTIVA® (efavirenz) is an HIV-1-specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Efavirenz is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-(3H)-trifluorothiazol-2-yl 3,1-benzoxazin-2-one. Its empirical formula is C_{19}H_{24}ClF_{3}NO_{2}, and its structural formula is:

![Structural formula of efavirenz]

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

Capsules: SUSTIVA is available as capsules for oral administration containing either 50 mg or 200 mg of efavirenz and the following inactive ingredients: lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium starch glycinate. The capsule shells may also contain silicon dioxide. The capsules are printed with ink containing gelatin, sodium lauryl sulfate, titanium dioxide, and/or yellow iron oxide. The capsule shells are containing purified cellulose, and sodium lauryl sulfates.

Tablets: SUSTIVA is available as film-coated tablets for oral administration containing 600 mg of efavirenz and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The film coating contains Opadry Yellow and hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium starch.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Efavirenz is an antiviral drug (see Clinical Pharmacology (12.4)).

12.3 Pharmacokinetics
Absorption
Peak efavirenz plasma concentrations of 1.6-9.1 μM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. In HIV-1-infected patients at steady state, mean C_{max}, mean C_{min}, and mean AUC were dose proportional following 200-mg, 400-mg, and 600-mg daily doses. Time-to-peak plasma concentrations were approximately 3-5 hours and steady-state plasma concentrations were reached in 6-10 days. In 35 patients receiving SUSTIVA 600 mg once daily, steady-state C_{max} was 12.9 ± 3.7 μM (mean ± SD), steady-state C_{min} was 5.6 ± 3.2 μM, and AUC was 184 ± 73 μM•h.

Effect of Food on Oral Absorption:
Capsules: Administration of a single 600-mg dose of efavirenz capsules with a high-fat/high-caloric meal (894 kcal, 54 g fat, 54% calories from fat) or a reduced-fat/normal-calorie meal (440 kcal, 2 g fat, 4% calories from fat) was associated with a mean increase of 22% and 17% in efavirenz AUC, and a mean increase of 39% and 51% in efavirenz C_{max}, respectively, relative to the exposures achieved when given under fasted conditions. See Dosage and Administration (2) and Patient Counseling Information (17.3).

Tablet: Administration of a single 600-mg efavirenz tablet with a high-fat/high-caloric meal (approximately 1000 kcal, 500-600 kcal from fat) was associated with a 28% increase in mean AUC of efavirenz and a 79% increase in mean C_{max} of efavirenz relative to the exposures achieved under fasted conditions. See Dosage and Administration (2) and Patient Counseling Information (17.3).

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 SUSTIVA 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.

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

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

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

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

Drug Interaction Studies
Efavirenz has been shown in vivo to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A. In vitro studies have shown that efavirenz inhibited CYP isozymes 2C9, 2C19, and 3A4 with Ki values (39-17 μM) in the range of observed efavirenz plasma concentrations. In in vitro studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (Ki values 82-160 μM) only at concentrations well above those achieved clinically. The inhibitory effect on CYP3A is expected to be similar between 200-mg, 400-mg, and 600-mg doses of efavirenz. Co-administration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Drug interaction studies were performed with efavirenz and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of efavirenz on the C_{max}, AUC, and C_{min} are summarized in Table 8 (effect of efavirenz on other drugs) and Table 9 (effect of other drugs on efavirenz). For information regarding clinical recommendations see Contraindications (4.2) and Drug Interactions (7.1).

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

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose</th>
<th>Efavirenz</th>
<th>Number of Subjects</th>
<th>C_{max} (90% CI)</th>
<th>AUC (90% CI)</th>
<th>C_{min} (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>400 mg qd</td>
<td>light meal</td>
<td>1-20</td>
<td>600 mg qd with a light meal</td>
<td>7-20</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>400 mg qd</td>
<td>light meal</td>
<td>7-14</td>
<td>600 mg qd with a light meal</td>
<td>7-20</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>300 mg qd</td>
<td>light meal</td>
<td>7-14</td>
<td>600 mg qd with a light meal</td>
<td>7-20</td>
<td>14</td>
</tr>
<tr>
<td>Indinavir</td>
<td>1000 mg qid</td>
<td>light meal</td>
<td>10 x 10</td>
<td>600 mg qd x 10</td>
<td>20</td>
<td>After</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>morning dose</td>
<td></td>
<td>After</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>afternoon dose</td>
<td></td>
<td>After</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>evening dose</td>
<td></td>
<td>After</td>
</tr>
</tbody>
</table>

1 Indicates increase. ▼ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%. a Compared with atazanavir 400 mg qd alone. b Comparator dose of indinavir was 800 mg qid x 10 days. c Parallel-design group; for efavirenz + lopinavir/ritonavir, n for lopinavir/ritonavir alone. d Values are for lopinavir; the pharmacokinetics of ritonavir in this study were unaffected by concurrent efavirenz. e 95% CI. f Soft Gelfoam Capsule. g Trend was not available. h Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg q12h for 2 days). i Not available because of insufficient data. NA = not available.

(Continued)
### SUSTIVA® (efavirenz)

#### Coadministered Drug Plasma Cmax, AUC, and Cmin

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose</th>
<th>Efavirenz Dose</th>
<th>Number of Subjects</th>
<th>Coadministered Drug Dose (mean % change)</th>
<th>Coadministered Drug</th>
<th>Efavirenz Dose</th>
<th>Number of Subjects</th>
<th>Cmin (90% CI)</th>
<th>AUC (90% CI)</th>
<th>Cmax (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>400 mg single dose</td>
<td>600 mg</td>
<td>9</td>
<td>NA</td>
<td>12</td>
<td>↓ 11%</td>
<td>9 (28-46%)</td>
<td>12</td>
<td>64%</td>
<td>44-57%</td>
</tr>
<tr>
<td></td>
<td>600 mg</td>
<td>9 days</td>
<td>23</td>
<td>NA</td>
<td>6</td>
<td>↓ 36%</td>
<td>36% (28-44%)</td>
<td>14</td>
<td>12%</td>
<td>69-75%</td>
</tr>
<tr>
<td></td>
<td>200 mg bid</td>
<td>3 days</td>
<td>600 mg</td>
<td>1</td>
<td>12</td>
<td>↓ 36%</td>
<td>36% (28-44%)</td>
<td>14</td>
<td>12%</td>
<td>69-75%</td>
</tr>
</tbody>
</table>

#### Table 8: Effect of Efavirenz on Coadministered Drug Plasma Cmax, AUC, and Cmin

**Continued**

### SUSTIVA® (efavirenz)

#### Effect of Coadministered Drug on Efavirenz Plasma Cmax, AUC, and Cmin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Efavirenz Dose</th>
<th>Number of Subjects</th>
<th>Coadministered Drug Dose (mean % change)</th>
<th>Coadministered Drug</th>
<th>Efavirenz Dose</th>
<th>Number of Subjects</th>
<th>Cmin (90% CI)</th>
<th>AUC (90% CI)</th>
<th>Cmax (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>400/100 mg capsule</td>
<td>600 mg</td>
<td>9</td>
<td>NA</td>
<td>12</td>
<td>↓ 11%</td>
<td>9 (28-46%)</td>
<td>12</td>
<td>64%</td>
<td>44-57%</td>
</tr>
<tr>
<td></td>
<td>40 mg single dose</td>
<td>600 mg</td>
<td>9</td>
<td>NA</td>
<td>6</td>
<td>↓ 36%</td>
<td>36% (28-44%)</td>
<td>14</td>
<td>12%</td>
<td>69-75%</td>
</tr>
<tr>
<td></td>
<td>200 mg bid</td>
<td>3 days</td>
<td>600 mg</td>
<td>1</td>
<td>12</td>
<td>↓ 36%</td>
<td>36% (28-44%)</td>
<td>14</td>
<td>12%</td>
<td>69-75%</td>
</tr>
</tbody>
</table>

#### Table 9: Effect of Efavirenz on Coadministered Drug Plasma Cmax, AUC, and Cmin

**Continued**
Efavirenz (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, nefaviren, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. EFV demonstrated additive to antagonistic antiviral activity in cell culture with stavudine. 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 humans receiving the 600-mg/day dose. The exposure in rats was lower than that in humans. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicity assays, efavirenz showed no evidence of mutagenic or clastogenic activity in a battery of in vitro and in vivo studies. These included bacterial mutation assays in S. typhimurium and E. coli, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an in vivo mouse bone marrow micronucleus assay. Given the lack of genotoxic activity of efavirenz, the relevance to humans of neoplasms in efavirenz-treated mice is not known. EFV did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

13.2 Animal Toxicology

Nonsustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose [see Warnings and Precautions (5.9)].

14 CLINICAL STUDIES

Study 006, a randomized, open-label trial, compared SUSTIVA (600 mg once daily) + zidovudine (ZDV, 300 mg q12h) + lamivudine (LAM, 150 mg q12h) or SUSTIVA (600 mg once daily) + indinavir (IDV, 1000 mg q12h) with indinavir (800 mg q8h) + zidovudine (300 mg q12h) + lamivudine (150 mg q12h). Twelve hundred sixty-six patients (mean age 36.5 years [range 18-81], 60% Caucasian, 33% male) were enrolled. All patients were efavirenz-, lamivudine-, NNRTI-, and PI-naïve at study entry. The median baseline CD4+ cell count was 320 cells/mm3 and the median baseline HIV-1 RNA level was 4.8 log10 copies/mL. Treatment outcomes with standard assay (assay limit 400 copies/mL) through 48 and 168 weeks are shown in Table 10. Plasma HIV RNA levels were quantified with standard assay and 400 copies/mL and ultrasensitive assay versions of the AMPLICOR HIV-1 MONITOR assay. During the study, version 1.5 of the assay was introduced in Europe to enhance detection of nonclade B virus.

12.4 Microbiology

Mechanism of Action

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

Antiviral Activity in Cell Culture

The concentration of EFV inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90-95% (EC90,95) ranged from 1.7 to 25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/monoocyte cultures. EFV demonstrated antiviral activity against clade B and most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses. EFV demonstrated additive antiviral activity without cytoxicity 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, nefaviren, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. EFV demonstrated additive to antagonistic antiviral activity in cell culture with stavudine. 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.

Table 9: Effect of Coadministered Drug on Efavirenz Plasma Cmax, AUC, and Cmin

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose</th>
<th>Efavirenz Dose</th>
<th>Number of Subjects</th>
<th>Cmax (90% CI)</th>
<th>AUC (90% CI)</th>
<th>Cmin (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>400 mg po x 2 / day, then 200 mg po q12h for 8 days</td>
<td>400 mg po x 2 / day, then 200 mg po q12h for 8 days</td>
<td>14</td>
<td>↑ 21% (95-56%)</td>
<td>↓ 36% (32-40%)</td>
<td>↓ 47% (41-53%)</td>
</tr>
<tr>
<td>Famotidine</td>
<td>40 mg x 4 days</td>
<td>40 mg x 4 days</td>
<td>14</td>
<td>↑ 12% (7-21%)</td>
<td>↓ 13% (5-18%)</td>
<td>↓ 13% (1-26%)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20 mg x 14 days</td>
<td>20 mg x 14 days</td>
<td>12</td>
<td>↑ 16% (8-26%)</td>
<td>↑ 11% (5-18%)</td>
<td>↑ 13% (1-26%)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50 mg x 14 days</td>
<td>50 mg x 14 days</td>
<td>13</td>
<td>↑ 11% (6-16%)</td>
<td>↑ 11% (6-16%)</td>
<td>↑ 11% (6-16%)</td>
</tr>
</tbody>
</table>
SUSTIVA® (efavirenz)

Table 10: Outcomes of Randomized Treatment Through 48 and 168 Weeks, Study 006

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Week 48</th>
<th>Week 160</th>
<th>Week 48</th>
<th>Week 160</th>
<th>Week 48</th>
<th>Week 160</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responderd</td>
<td>69%</td>
<td>48%</td>
<td>57%</td>
<td>40%</td>
<td>50%</td>
<td>29%</td>
</tr>
<tr>
<td>Virologic failureb</td>
<td>6%</td>
<td>12%</td>
<td>15%</td>
<td>20%</td>
<td>13%</td>
<td>19%</td>
</tr>
<tr>
<td>Discontinued for adverse events</td>
<td>7%</td>
<td>8%</td>
<td>6%</td>
<td>8%</td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td>Discontinued for other reasonsd</td>
<td>17%</td>
<td>31%</td>
<td>22%</td>
<td>32%</td>
<td>21%</td>
<td>32%</td>
</tr>
</tbody>
</table>

CD4+ cell count (cells/mm³)

- Observed subjects (n): 279, 205, 256, 158, 228, 129
- Mean change from baseline: 190, 329, 191, 319, 180, 329

- Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 or Week 168.
- 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.
- Includes consent withdrawn, lost to follow-up, noncompliance, never treated, missing data, protocol violation, death, and other reasons.

ACTG 364 is a randomized, double-blind, placebo-controlled, 48-week study in NRTI-experienced patients who had completed two prior ACTG studies. One-hundred ninety-six patients (mean age 41 years [range 18–76], 74% Caucasian, 88% male) received NRTIs in combination with SUSTIVA (efavirenz) (600 mg once daily), or nefinavir (NFI, 750 mg three times daily), or SUSTIVA (600 mg once daily) + nefinavir in a randomized, double-blinded manner. The mean baseline CD4+ cell count was 389 cells/mm³ and mean baseline HIV-1 RNA level was 8130 copies/mL. Upon entry into the study, all patients were assigned a new open-label NRTI regimen, which was dependent on their previous NRTI treatment experience. There was no significant difference in the mean CD4+ cell count among treatment groups; the overall mean increase was approximately 100 cells at 48 weeks among patients who continued on the study regimens. Treatment outcomes are shown in Table 11. Plasma HIV RNA levels were quantified with the AMPLICOR HIV-1 MONITOR assay using a lower limit of quantification of 500 copies/mL.

Table 11: Outcomes of Randomized Treatment Through 48 Weeks, Study ACTG 364*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Week 48 (n=422)</th>
<th>Week 48 (n=429)</th>
<th>Week 48 (n=413)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt;500 copies/mL</td>
<td>71%</td>
<td>63%</td>
<td>41%</td>
</tr>
<tr>
<td>HIV-1 RNA ≥500 copies/mL</td>
<td>17%</td>
<td>34%</td>
<td>54%</td>
</tr>
<tr>
<td>CDC Category C Event</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Discontinuations for adverse events</td>
<td>3%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Discontinuations for other reasons</td>
<td>8%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

- Subjects achieved virologic response (two consecutive viral loads <500 copies/mL) and maintained it through Week 48.
- Includes viral rebound and failure to achieve confirmed <500 copies/mL by Week 48.

- See Adverse Reactions (6.1) for a safety profile of these regimens.
- Includes loss to follow-up, consent withdrawn, noncompliance.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Capsules

SUSTIVA® (efavirenz) capsules are available as follows:
- Capsules 200 mg are gold color, reverse printed with “SUSTIVA” on the body and imprinted “200 mg” on the cap. Bottles of 90 NDC 0056-0474-92
- Capsules 50 mg are gold color and white, printed with “SUSTIVA” on the gold color cap and reverse printed “50 mg” on the white body. Bottles of 30 NDC 0056-0470-30

16.2 Tablets

SUSTIVA® (efavirenz) tablets are available as follows:
- Tablets 800 mg are yellow, capsule-shaped, film-coated tablets, with “SUSTIVA” printed on both sides.
- Bottles of 30 NDC 0056-0510-30

16.3 Storage

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

17.1 Drug Interactions

A statement to patients and healthcare providers is included on the product’s bottle labels: ALERT: Find out about medicines that should NOT be taken with SUSTIVA.

SUSTIVA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products, particularly St. John’s wort.

17.2 General Information for Patients

Patients should be informed that SUSTIVA is not a cure for HIV-1 infection and that they may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician while taking SUSTIVA. Patients should be told that the use of SUSTIVA has not been shown to reduce the risk of transmitting HIV-1 to others through sexual contact or blood contamination.

17.3 Dosing Instructions

Patients should be advised to take SUSTIVA every day as prescribed. SUSTIVA must always be used in combination with other antiretroviral drugs. Patients should be advised to take SUSTIVA on an empty stomach, preferably at bedtime. Taking SUSTIVA with food increases efavirenz concentrations and may increase the frequency of adverse reactions. Dosing at bedtime may improve the tolerability of nervous system symptoms [see Dosage and Administration (2) and Adverse Reactions (6.1)].

17.4 Nervous System Symptoms

Patients should be informed that central nervous system symptoms (NSS) including dizziness, insomnia, impaired concentration, drowsiness, and abnormal dreams are commonly reported during the first weeks of therapy with SUSTIVA [see Warnings and Precautions (5.5)]. Dosing at bedtime may improve the tolerability of these symptoms, which are likely to improve with continued therapy. Patients should be alerted to the potential for additive effects when SUSTIVA is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience NSS they should avoid potentially hazardous tasks such as driving or operating machinery.

17.5 Psychiatric Symptoms

Patients should be informed that serious psychiatric symptoms including severe depression, suicidal ideation, aggressive behavior, delusions, paranoia, and psychosis-like symptoms have been reported in patients receiving SUSTIVA [see Warnings and Precautions (5.4)]. If they experience severe psychiatric adverse experiences they should seek immediate medical evaluation. Patients should be advised to inform their physician of any history of mental illness or substance abuse.

17.6 Rash

Patients should be informed that a common side effect is rash [see Warnings and Precautions (5.7)]. Rashes usually go away without any change in treatment. However, since rash may be serious, patients should be advised to contact their physician promptly if rash occurs.

17.7 Reproductive Risk Potential

Women receiving SUSTIVA should be instructed to avoid pregnancy [see Warnings and Precautions (5.6)]. A reliable form of barrier contraception must always be used in combination with other methods of contraception, including oral or other hormonal contraception. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of SUSTIVA is recommended. Women should be advised to notify their physician if they become pregnant or plan to become pregnant while taking SUSTIVA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential harm to the fetus.

17.8 Fat Redistribution

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known [see Warnings and Precautions (5.12)].
SUSTIVA® (efavirenz) Capsules and tablets

ALERT: Find out about medicines that should NOT be taken with SUSTIVA. Please also read the section “MEDICATIONS YOU SHOULD NOT TAKE WITH SUSTIVA.”

Read this information before you start taking SUSTIVA. Read it again each time you refill your prescription, in case there is any new information. This leaflet provides a summary about SUSTIVA and does not include everything there is to know about your medicine. This information is not meant to take the place of talking with your doctor.

What is SUSTIVA?
SUSTIVA is a medicine used in combination with other medicines to help treat infection with Human Immunodeficiency Virus type 1 (HIV-1), the virus that causes AIDS (acquired immune deficiency syndrome). SUSTIVA is a type of anti-HIV drug called a “non-nucleoside reverse transcriptase inhibitor” (NNRTI). NNRTIs are not used in the treatment of Human Immunodeficiency Virus type 2 (HIV-2) infection.

SUSTIVA is a medicine used in combination with other medicines to help treat infection with Human Immunodeficiency Virus type 1 (HIV-1), the virus that causes AIDS (acquired immune deficiency syndrome). SUSTIVA is a type of anti-HIV drug called a “non-nucleoside reverse transcriptase inhibitor” (NNRTI). NNRTIs are not used in the treatment of Human Immunodeficiency Virus type 2 (HIV-2) infection.

SUSTIVA works by lowering the amount of HIV-1 in the blood (viral load). SUSTIVA must be taken with other anti-HIV medicines. When taken with other anti-HIV medicines, SUSTIVA has been shown to reduce viral load and increase the number of CD4+ cells, a type of immune cell in blood. SUSTIVA may not have these effects in every patient.

SUSTIVA does not cure HIV or AIDS. People taking SUSTIVA may still develop other infections and complications. Therefore, it is very important that you stay under the care of your doctor.

SUSTIVA has not been shown to reduce the risk of passing HIV to others. Therefore, continue to practice safe sex, and do not use or share dirty needles.

What are the possible side effects of SUSTIVA?
Serious psychiatric problems. A small number of patients experience severe depression, strange thoughts, or angry behavior while taking SUSTIVA. Some patients have thoughts of suicide and a few have actually committed suicide. These problems tend to occur more often in patients who have had mental illness. Contact your doctor right away if you think you are having these psychiatric symptoms, so your doctor can decide if you should continue to take SUSTIVA (efavirenz).

Common side effects. Many patients have dizziness, trouble sleeping, drowsiness, trouble concentrating, and/or unusual dreams during treatment with SUSTIVA. These side effects may be reduced if you take SUSTIVA at bedtime on an empty stomach. They also tend to go away after you have taken the medicine for a few weeks. If you have these common side effects, such as dizziness, it does not mean that you will also have serious psychiatric problems, such as severe depression, strange thoughts, or angry behavior. Tell your doctor right away if any of these side effects continue or if they bother you. It is possible that these symptoms may be more severe if SUSTIVA is used with alcohol or mood altering (street) drugs.

If you are dizzy, have trouble concentrating, or are drowsy, avoid activities that may be dangerous, such as driving or operating machinery.

Rash is common. Rashes usually go away without any change in treatment. In a small number of patients, rash may be serious. If you develop a rash, call your doctor right away. Rash may be a serious problem in some children. Tell your child’s doctor right away if you notice rash or any other side effects while your child is taking SUSTIVA. The dose of SUSTIVA for children may be lower (see Can children take SUSTIVA?).

Other common side effects include tiredness, upset stomach, vomiting, and diarrhea. Some patients taking SUSTIVA have experienced increased levels of lipids (cholesterol and triglycerides) in the blood.

Changes in body fat. Changes in body fat develop in some patients taking anti-HIV medicine. These changes may include an increased amount of fat in the upper back and neck (“buffalo hump”), in the breasts, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these fat changes are not known.

Tell your doctor or healthcare provider if you notice any side effects while taking SUSTIVA.

Changing your doctor. If you take SUSTIVA because of side effects or for any other reason.

This is not a complete list of side effects possible with SUSTIVA. Ask your doctor or pharmacist for a more complete list of side effects of SUSTIVA and all the medicines you will take.

How should I take SUSTIVA?

General Information

• You should take SUSTIVA on an empty stomach, preferably at bedtime.

• Swallow SUSTIVA with water.

• Taking SUSTIVA with food increases the amount of medicine in your body, which may increase the frequency of side effects.

• Taking SUSTIVA at bedtime may make some side effects less bothersome.

• SUSTIVA must be taken in combination with other anti-HIV medicines. If you take only SUSTIVA, the medicine may stop working.

Do not miss a dose of SUSTIVA. If you forget to take SUSTIVA, take the missed dose right away, unless it is almost time for your next dose. Do not double the next dose. Carry on with your regular dosing schedule. If you need help in planning the best times to take your medicine, ask your doctor or pharmacist.

Take the exact amount of SUSTIVA your doctor prescribes. Never change the dose on your own. Do not stop this medicine unless your doctor tells you to stop.

• If you believe you took more than the prescribed amount of SUSTIVA, contact your local Poison Control Center or emergency room right away.

• Tell your doctor if you start any new medicine or change how you take old ones. Your doses may need adjustment.

• When your SUSTIVA supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to SUSTIVA and become harder to treat.

• Your doctor may want to do blood tests to check for certain side effects while you take SUSTIVA (efavirenz).

Capsules

• The dose of SUSTIVA capsules for adults is 600 mg (three 200-mg capsules, taken together) once a day by mouth. The dose of SUSTIVA for children may be lower (see Can children take SUSTIVA?).

Tablets

• The dose of SUSTIVA tablets for adults is 600 mg (one tablet) once a day by mouth.

Can children take SUSTIVA?

Yes, children who are able to swallow capsules can take SUSTIVA. Rash may be a serious problem in some children. Tell your child’s doctor right away if you notice rash or any other side effects while your child is taking SUSTIVA. The dose of SUSTIVA for children may be lower than the dose for adults. Capsules containing lower doses of SUSTIVA are available. Your child’s doctor will determine the right dose based on your child’s weight.

Who should not take SUSTIVA?

Do not take SUSTIVA if you are allergic to the active ingredient, efavirenz, or to any of the inactive ingredients. Your doctor and pharmacist have a list of the inactive ingredients.

What should I avoid while taking SUSTIVA?

• Women should not become pregnant while taking SUSTIVA and for 12 weeks after stopping it. Serious birth defects have been seen in the offspring of animals and women treated with SUSTIVA during pregnancy. It is not known whether SUSTIVA caused these defects. Tell your doctor right away if you are pregnant. Also talk with your doctor if you want to become pregnant.

• Women should not rely only on hormone-based birth control, such as pills, injections, or implants, because SUSTIVA may make these contraceptives ineffective. Women must use a reliable form of barrier contraception, such as a condom or diaphragm, even if they also use other methods of birth control. SUSTIVA may remain in your blood for a time after therapy is stopped. Therefore, you should continue to use contraceptive measures for 12 weeks after you stop taking SUSTIVA.

• Do not breast-feed if you are taking SUSTIVA. The Centers for Disease Control and Prevention recommend that mothers with HIV not breast-feed because they can pass the HIV through their milk to the baby. Also, SUSTIVA may pass through breast milk and cause serious harm to the baby. Talk with your doctor if you are breast-feeding. You may need to stop breast-feeding or use a different medicine.

• Taking SUSTIVA with alcohol or other medicines causing similar side effects as SUSTIVA, such as drowsiness, may increase those side effects.

• Do not take any other medicines without checking with your doctor. These medicines include prescription and nonprescription medicines and herbal products, especially St. John’s wort (Hypericum perforatum).

Before using SUSTIVA, tell your doctor if you

• have problems with your liver or have hepatitis. Your doctor may want to do tests to check your liver while you take SUSTIVA.

• have ever had mental illness or are using drugs or alcohol.

• have ever had seizures or are taking medicine for seizures [for example, Dilantin (phenytoin), Tegretol (carbamazepine), or phenobarbital]. Your doctor may want to switch you to another medicine or check drug levels in your blood from time to time.

What important information should I know about taking other medicines with SUSTIVA?

SUSTIVA may change the effect of other medicines, including ones for HIV, and cause serious side effects. Your doctor may change your other medicines or change their doses. Other medicines, including herbal products, may affect SUSTIVA. For this reason, it is very important to:

• let all your doctors and pharmacists know that you take SUSTIVA.

• tell your doctors and pharmacists about all medicines you take. This includes those you buy over-the-counter and herbal or natural remedies.
Bring all your prescription and nonprescription medicines as well as any herbal remedies that you are taking when you see a 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 medicines you use. Then he or she can decide the best approach for your situation.

Taking SUSTIVA with St. John's wort (Hypericum perforatum), an herbal product sold as a dietary supplement, or products containing St. John's wort is not recommended. Talk with your doctor if you are taking or are planning to take St. John's wort. Taking St. John's wort may decrease SUSTIVA levels and lead to increased viral load and possible resistance to SUSTIVA or cross-resistance to other anti-HIV drugs.

MEDICINES YOU SHOULD NOT TAKE WITH SUSTIVA

The following medicines may cause serious and life-threatening side effects when taken with SUSTIVA. You should not take any of these medicines while taking SUSTIVA:

• Vascor (bepridil)
• Propulsid (cisapride)
• Versed (midazolam)
• Orap (pimozide)
• Halcion (triazolam)
• Ergot medications (for example, Wigraine and Cafergot)

The following medicine should not be taken with SUSTIVA since it contains efavirenz, the active ingredient in SUSTIVA:
• ATRIPLA (efavirenz, emtricitabine, tenofovir disoproxil fumarate)

The following medicines may need to be replaced with another medicine when taken with SUSTIVA:

• Fortovase, Inavirsa (saquinavir)
• Biaxin (clarithromycin)
• Carbortol, Tegretol (carbamazepine)
• Sporanox (itraconazole)
• REYATAZ (atazanavir sulfate), if this is not the first time you are receiving treatment for your HIV infection

The following medicines may require a change in the dose of either SUSTIVA or the other medicine:

• Calcium channel blockers such as Cardizem or Tiazac (diltiazem), Covera HS or Isotin SR (verapamil), and others.
• The cholesterol-lowering medicines Lipitor (atorvastatin), PRAVACHOL (pravastatin sodium), and Zocor (simvastatin).
• Crixivan (indinavir)
• Kaletra (lopinavir/ritonavir)
• Methadone
• Mycobutin (rifabutin)
• REYATAZ (atazanavir sulfate). If you are taking SUSTIVA and REYATAZ, you should also be taking Norvir (ritonavir).
• Rifadin (rifampin) or the rifampin-containing medicines Rifamate and Rifater.
• Vfend (itraconazole) and SUSTIVA must not be taken together at standard doses. Some doses of voriconazole can be taken at the same time as a lower dose of SUSTIVA, but you must check with your doctor first.
• Zoloft (sertraline)
• The immunosuppressant medicines cyclosporine (Gengraf, Neoral, Sandimmune, and others), Prograf (tacrolimus), or Rapamune (sirolimus).

These are not all the medicines that may cause problems if you take SUSTIVA. Be sure to tell your doctor about all medicines that you take.