Bristol-Myers Squibb Company

March 2005

**Re: Important Change in SUSTIVA® (efavirenz) Package Insert — Change from Pregnancy Category C to D**

Dear Health Care Provider,

Bristol-Myers Squibb Company would like to make clinicians who are caring for HIV-1-infected patients aware of important new information in the SUSTIVA Package Insert regarding pregnancy. **The pregnancy category for SUSTIVA has been changed from Category C (Risk of Fetal Harm Cannot Be Ruled Out) to Category D (Positive Evidence of Fetal Risk).** This change is a result of four retrospective reports of neural tube defects in infants born to women with first trimester exposure to SUSTIVA including three cases of meningomyelocele and one Dandy Walker Syndrome. **As SUSTIVA may cause fetal harm when administered during the first trimester to a pregnant woman, pregnancy should be avoided in women receiving SUSTIVA.**

Women of childbearing potential should undergo pregnancy testing before initiation of SUSTIVA. If SUSTIVA 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. Though there are no adequate, well-controlled studies in pregnant women, SUSTIVA should be used during the first trimester of pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options. Barrier contraception should always be used in combination with other contraceptive methods.

During the development of SUSTIVA, animal studies were performed to assess the potential for birth defects. Malformations were 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 resulting in plasma drug concentrations similar to those in humans given 600 mg/day of SUSTIVA. Anencephaly and unilateral anophthalmia were observed in one monkey fetus, microophthalmia 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. An increase in fetal resorptions was observed in rats given efavirenz doses that produced peak plasma concentrations and area under the curve (AUC) values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of SUSTIVA. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans given 600 mg once daily of SUSTIVA.

Limited data are available regarding birth defects occurring after intrauterine exposure to SUSTIVA. The outcomes of pregnancy have been reviewed for 206 women (207 fetuses) after being exposed to efavirenz-containing regimens, most of which were first-trimester exposures. Birth defects occurred in 5 of 188 live births with first-trimester exposure and in 0 of 13 live births with second- or third-trimester exposure. None of these prospectively reported defects were neural tube defects. However, there have been 4 retrospective reports (i.e., after the results of the pregnancy were known) of findings consistent with neural tube defects, including 3 cases of meningomyelocele. All 4 mothers were exposed to efavirenz-containing regimens in the first trimester. Although

a causal relationship of these events to the use of SUSTIVA has not been established, similar defects have been observed in preclinical studies of efavirenz.

**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 (800) 258-4263.

Please refer to the accompanying Important Information about SUSTIVA and the enclosed SUSTIVA Full Prescribing Information.

If you have any questions about this new information or require additional medical information, please contact the Virology Medical Services Department at Bristol-Myers Squibb Company at 1-800-426-7644 (select Option 3).

Sincerely,

Freda C. Lewis-Hall, MD
Senior Vice President, Medical Affairs
Bristol-Myers Squibb Company

SUSTIVA is a registered trademark of Bristol-Myers Squibb Pharma Company.

Enclosure: SUSTIVA® (efavirenz) Package Insert

## REFERENCE

1. SUSTIVA Package Insert, Bristol-Myers Squibb Co., Princeton, New Jersey.

# Important Information About SUSTIVA® (efavirenz) Capsules and Tablets

**INDICATION:**

SUSTIVA (efavirenz) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on two clinical trials of at least one year duration that demonstrated prolonged suppression of HIV RNA.

**IMPORTANT SAFETY INFORMATION:**

- Coadministration with astemizole, cisapride, midazolam, triazolam, ergot derivatives, or voriconazole is contraindicated. Concomitant use of SUSTIVA and St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products is not recommended. **This list of medications is not complete.**
- Serious psychiatric adverse experiences, including severe depression (2.4%), have been reported in patients treated with SUSTIVA. In addition to SUSTIVA, factors identified in a clinical study that were associated with an increase in psychiatric symptoms included history of injection drug use, psychiatric history, and use of psychiatric medication. There have been occasional reports of suicide, delusions, and psychosis-like behavior, but it could not be determined if SUSTIVA was the cause. Patients with serious psychiatric adverse experiences should be evaluated immediately to determine whether the risks of continued therapy outweigh the benefits.
- Fifty-three percent of patients reported nervous system symptoms when taking SUSTIVA compared to 25% of patients receiving control regimens. These symptoms usually begin during Days 1-2 of therapy and generally resolve after the first 2-4 weeks of therapy. Nervous system symptoms are not predictive of less frequent serious psychiatric symptoms.
- SUSTIVA may cause fetal harm when administered to a pregnant woman. Women should not become pregnant or breastfeed while taking SUSTIVA. Barrier contraception must always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). If a woman becomes pregnant while taking SUSTIVA during the first trimester of pregnancy, she should be apprised of the potential harm to the fetus.
- Mild to moderate rash is a common side effect of SUSTIVA. In controlled clinical trials, 26% of patients treated with SUSTIVA experienced new-onset skin rash compared with 17% of patients treated in control groups. SUSTIVA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Rash is more common and often more severe in pediatric patients.
- Liver enzymes should be monitored in patients with known or suspected hepatitis B or C and when SUSTIVA is administered with ritonavir.
- Use SUSTIVA with caution in patients with a history of seizures.
- Redistribution and/or accumulation of body fat have been seen in patients receiving antiretroviral therapy. A causal relationship has not been established.
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including SUSTIVA.
- It is recommended that SUSTIVA be taken on an empty stomach, preferably at bedtime. The increased concentrations following administration of SUSTIVA with food may lead to an increase in frequency of adverse events. Dosing at bedtime may improve the tolerability of nervous system symptoms.

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