FDA Downgrades the Antiviral Efavirenz to Pregnancy Category D

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The Food and Drug Administration has downgraded efavirenz to pregnancy category D. "Positive Evidence of Fetal Risk," is urging women to avoid being pregnant while taking the anti-retroviral drug.

The new package label stems from four retrospective reports of women who gave birth to infants with neural tube defects after first-trimester exposure to efavirenz (Sustiva). Three infants were diagnosed with meningomyelocele and one with Dandy Walker syndrome.

Physicians are being asked to report pregnant patients who have been exposed to efavirenz to the Antiretroviral Pregnancy Registry (800-258-4263), which is established to monitor fetal outcomes.

The drug had previously been labeled category C. "Risk of Fetal Harm Cannot Be Ruled Out." Butrow-Myers, Swiggub Co., Princeton, N.J., alerted health care providers to the label change in a letter dated March 2003 and made public in June. Signed by Freda C. Lewis-Hall, M.D., senior vice president for medical affairs, the letter urged prenatal testing before women start on efavirenz.

"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," Dr. Lewis-Hall advised. "Barrier contraception should always be used in combination with other contraceptive methods."

Dr. Lewis-Hall described a prospective review of pregnancy outcomes for 206 women who carried 207 fetuses, while exposed to efavirenz. Fifty-six of 188 infants born after first-trimester exposure had birth defects; none were observed in 13 live births after second- or third-trimester exposures. Dr. Lewis-Hall did not describe the birth defects, except to say they were not neural tube defects, which, so far, have only been seen in retrospective reports.

"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," she wrote. Her letter cited a preclinical animal study that reported malformations in 3 of 20 fetuses from cynomologous monkeys treated with efavirenz throughout pregnancy.

Gerald G. Briggs, B.Pharm., told news media that he is concerned about the report, which he said was "not compelling." Mr. Briggs said, "But based on the potential signal, I would recommend the same folic acid dose used for anticonvulsants known to cause neural tube defects in women with a history of giving birth to an infant with a neural tube defect: 4 or 5 mg per day."