Dragon, Karen E. (CDC/NIOSH/EID)

From: Orlando, Eileen [eileen.orlando@bms.com]
Sent: Monday, October 03, 2011 1:21 PM
To: NIOSH Docket Office (CDC)
Subject: 190 - NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2012: Proposed Additions and Deletions to the NIOSH Hazardous Drug List
Attachments: NIOSH.pdf

Please see comments from Bristol-Myers Squibb.

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Think Before You Print

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September 27, 2011

National Institute of Occupational Safety and Health
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RE: NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2012: Proposed Additions and Deletions to the NIOSH Hazardous List

Bristol-Myers Squibb Co. appreciates the opportunity to comment concerning the draft 'NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2012: Proposed Additions and Deletions to the NIOSH Hazardous List'. Our one comment concerns the proposed addition of efavirenz to the list. During the 2007 update of the Hazardous Drug list, NIOSH proposed that efavirenz be added to the list. At that time Bristol-Myers Squibb Co. objected to the addition of efavirenz and provided comment. Subsequently, efavirenz was not added to the list. Please review the following comment regarding efavirenz.

Sustiva® (efavirenz)

Sustiva® (efavirenz) should not be identified as a hazardous drug on the updated list.

Sustiva® (efavirenz) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) being used for the treatment of HIV-1. Sustiva® (efavirenz) is supplied as capsules, tablets and an oral solution. There was equivocal evidence of tumors in rodent carcinogenicity studies. The mechanism of the carcinogenic potential is unknown. However, given the lack of genotoxic activity of Sustiva® (efavirenz) and the high doses used in the carcinogenicity studies, cancer is not considered an endpoint of concern with regard to the hazardous drug alert. To date, there is no known association linking efavirenz exposures to cancer in humans.

With respect to developmental toxicity, in monkeys, Sustiva® (efavirenz) at 60 mg/kg/day was administered to pregnant females throughout pregnancy (gestation days 20 through 150). The maternal systemic drug exposures (AUC) were 1.3 times the exposure in humans at the recommended clinical dose (600 mg/day), with fetal umbilical venous drug concentrations approximately 0.7 times the maternal values. Three fetuses of 20 fetuses/infants had one or more malformations; there were no malformed fetuses or infants from placebo-treated mothers. The malformations that occurred in these three monkey fetuses included anencephaly and unilateral anophthalmia in one fetus, microophthalmia in a second, and cleft palate in the third. There was no NOAEL (no observable adverse effect level) established for this study because only one dosage was evaluated. As of July 2010, the Antiretroviral Pregnancy Registry has received prospective reports of 792 pregnancies exposed to Sustiva® (efavirenz)-containing regimens, nearly all of which were first trimester exposures (718 pregnancies). Birth defects occurred in 17 of 604 live births (first trimester exposure) and 2 of 69 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 Sustiva® (efavirenz) has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic banding,

a known association with anophthalmia. There have been six retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to Sustiva® (efavirenz) containing regimens in the first trimester. Although a causal relationship of these events to the use of Sustiva® (efavirenz) has not been established, similar defects have been observed in preclinical studies of Sustiva® (efavirenz). The Sustiva® (efavirenz) high therapeutic dose of 600 mg/day is well above the NIOSH potent therapeutic dose cut off of 10 mg/day to be considered a Hazardous Drug. In animals, relatively high doses with systemic exposures greater than the therapeutic dose were required for organ toxicity and developmental toxicity (60 mg/kg/day) to occur. The evidence indicates that Sustiva® (efavirenz) has a low potential to result in any of these effects as a consequence of routine occupational contact. Given the high therapeutic dose of 600 mg/day, developmental toxicity, genotoxicity and organ toxicity are not considered endpoints of concern with regard to the hazardous drug alert. Reference: Sustiva® (efavirenz) USPI, Bristol-Myers Squibb Co., September 2011.
Conclusion: Sustiva® (efavirenz) does *not* meet the definition of a hazardous drug as per the definition in the NIOSH Hazardous Drug Alert.

Bristol-Myers Squibb Co. Appreciates the opportunity to provide this comment regarding the proposed inclusion of efavirenz on the updated list. Please contact the undersigned if any clarification or further information is needed.

Sincerely,

William McGrath, C.S.P., C.I.H.
Group Director
Research & Development EHS