IMPORTANT DRUG WARNING

January 5, 2001

Dear Healthcare Provider,

Fatal lactic acidosis has recently been reported in pregnant women treated throughout gestation with the combination of stavudine and didanosine. Based on these cases, the combination of stavudine (ZERIT®) and didanosine (VIDEX® or VIDEX® EC) should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk, such as when there are few remaining treatment options.

This recommendation is based on three cases of fatal lactic acidosis, two with and one without pancreatitis, that occurred in women who were either pregnant or postpartum and whose antiretroviral therapy during pregnancy included stavudine and didanosine in combination with other antiretroviral agents. Two of the infants of these women died, one in utero at 32 weeks gestation and one after emergency caesarian section at 36 weeks gestation. Two of the fatal cases occurred in patients enrolled in BMS study AI424-007, an open-label, multinational, randomized, two-arm comparison of stavudine plus didanosine plus nelfinavir (Viracept®) versus stavudine plus didanosine plus BMS-232632 (an investigational protease inhibitor). A third pregnancy-related death attributed to lactic acidosis was reported through worldwide postmarketing surveillance. This patient had received long-term therapy with stavudine and didanosine together with the NNRTI nevirapine (Viramune®). In addition, postmarketing surveillance identified several nonfatal cases of pancreatitis, with and without lactic acidosis or hepatic failure, in pregnant women receiving stavudine plus didanosine.

PATIENT MANAGEMENT

Stavudine and didanosine are nucleoside reverse transcriptase inhibitors indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. The nucleoside analogue class of antiretroviral drugs has been implicated in idiopathic lactic acidosis and severe hepatomegaly with steatosis, and all members of this class carry a warning in the label to this effect. Data have suggested that women may be at higher risk for these toxicities and it is unclear whether pregnancy potentiates these known side effects. However, the temporal occurrence of the three deaths should serve as a reminder that potential risks may be associated with use of these agents in pregnancy. Decisions regarding antiretroviral therapy for pregnant women are complex and should be made by healthcare providers experienced in the treatment of HIV infection. Although the VIDEX (didanosine), VIDEX EC (didanosine), and ZERIT (stavudine) labels have always advised of the risks of lactic acidosis, Bristol-Myers Squibb has decided to expand the **Boxed**

Warning, Warnings, and **Precautions** sections to reflect the new information that has been described above. For the complete Warning on lactic acidosis and the Precaution regarding the use of these agents in pregnancy, please see the enclosed full prescribing information.

The revised **Boxed Warning** statements for both the didanosine and stavudine labels are stated below:

> **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine (stavudine) and other antiretrovirals. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.**

Please see enclosed full prescribing information for VIDEX (didanosine), VIDEX EC (didanosine), and ZERIT (stavudine) for additional information regarding the recommended use of these agents.

If you have any further questions, please contact the Medical Information Department at Bristol-Myers Squibb Company at 1-800-426-7644.

Sincerely,

A. Collier Smyth, M.D.
Vice President, Medical Affairs