BMS Virology™
Bristol-Myers Squibb Company

IMPORTANT DRUG WARNING

February 2002

Dear Healthcare Provider,

Bristol-Myers Squibb Company would like to remind healthcare providers caring for persons with HIV of the potential for lactic acidosis as a complication of therapy with nucleoside analogues, including ZERIT® (stavudine), d4T. The early signs and symptoms of clinical events associated with hyperlactatemia should receive careful attention because of the life-threatening potential of the most extreme manifestation, lactic acidosis syndrome (LAS).

Bristol-Myers Squibb has received reports of rare occurrences of rapidly ascending neuromuscular weakness, mimicking the clinical presentation of Guillain-Barré syndrome (including respiratory failure), in HIV-infected patients receiving stavudine in combination with other antiretrovirals. Some cases were fatal. Most of the cases were reported in the setting of lactic acidosis or symptomatic hyperlactatemia and, in most, antiretroviral therapy had been continued in the presence of non-specific signs compatible with early symptomatic hyperlactatemia that preceded the development of neuromuscular signs and symptoms. If motor weakness develops in a patient receiving stavudine, the drug should be discontinued.

Confirmed elevations of serum lactate may be associated with a broad spectrum of clinical manifestations, ranging from asymptomatic hyperlactatemia, through symptomatic non-acidotic hyperlactatemia (SHL), to acute severe LAS. Early signs and symptoms associated with a high lactate may be subtle and include generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnea), or neurologic symptoms (including motor weakness). Patients with these symptoms should promptly interrupt antiretroviral therapy, and a full medical work-up should be performed rapidly.[i] Permanent discontinuation of stavudine should be considered for patients with confirmed LAS. It is important to note that symptoms associated with hyperlactatemia may continue or worsen following discontinuation of antiretroviral therapy.

At this time, prospective monitoring of lactate levels does not appear to be helpful in predicting the subsequent occurrence of SHL or LAS.[i]

Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine.[ii, iii, iv]

See the enclosed full prescribing information for ZERIT® for additional information regarding the recommended use of stavudine. If you have any further questions, please contact the Medical Information Department at Bristol-Myers Squibb Company at 1-800-426-7644.

Sincerely,

Michael R. Stevens

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i. Brinkman K. Management of hyperlactatemia: no need for routine lactate measurements. *AIDS* 2001; 15: 795-797.

ii. John M, Moore CB, James IR, et al. Chronic hyperlactatemia in HIV-infected patients taking antiretroviral therapy. *AIDS* 2001; 15: 717-723.

iii. Lonergan JT, Havlir D, Barber E, Mathews WC. Incidence and Outcome of Hyperlactatemia Associated with Clinical Manifestations in HIV-Infected Adults Receiving NRTI-Containing Regimens. 8th Conference on Retroviruses and Opportunistic Infections. Chicago, February 2001 [abstract 624].

iv. Gerard Y, Maulin L, et al. Symptomatic hyperlactatemia: an emerging complication of antiretroviral therapy. *AIDS* 2000; 14: 2723-2730.