# IMPORTANT DRUG WARNING

Dear Health Care Provider:

Bristol-Myers Squibb would like to advise you of a revised warning about fatal and non-fatal pancreatitis in the labeling for Videx® (didanosine, ddI), a nucleoside analogue reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Since its approval in 1991, the didanosine label has carried a warning about fatal and nonfatal pancreatitis. That warning was based on the incidence of pancreatitis found in Phase III trials in patients with very advanced HIV disease that ranged from 1% to 10% with doses higher than are currently recommended and 1% to 7% with the currently recommended dose. This letter is being provided because of deaths due to pancreatitis that have been reported from clinical trials studying the combination of didanosine plus stavudine (d4T) with and without hydroxyurea. These deaths occurred both in patients who were treatment-experienced and treatment- naïve without significant immunosuppression, and at the recommended doses of didanosine and stavudine. Use of hydroxyurea for the treatment of HIV infection is not approved by the FDA and is considered investigational.

**SUMMARY OF REPORTS**

- Two treatment-naive patients died of pancreatitis approximately seven months after initiation of treatment with didanosine plus stavudine and a protease inhibitor in two clinical trials.

- Two deaths due to pancreatitis occurred among 68 previously-treated patients enrolled in an arm of the ACTG 5025 study which utilized didanosine with hydroxyurea (600 mg BID) plus stavudine and indinavir. Both patients were hospitalized for pancreatitis within three months of enrollment and died one to ten weeks after diagnosis. Although a formal causal relationship was not established, the ACTG 5025 trial was subsequently terminated due to the higher risk of several toxicities, including fatal and non-fatal pancreatitis, in this treatment group.

- All of these patients had $CD_4$ >500 cells/μL and HIV RNA <200 copies/mL.

- Three of the four patients who died had additional risk factors for pancreatitis, including morbid obesity, hypertriglyceridemia, and cholelithiasis.

- In addition, deaths due to pancreatitis in patients treated with didanosine have been reported to the FDA MedWatch program. Since 1998, the majority of these reports have been in patients who were also receiving stavudine with and without hydroxyurea.

## PATIENT MANAGEMENT

The clinical outcome of pancreatitis may be improved by early identification of the clinical and laboratory signs and symptoms of pancreatitis (abdominal pain, nausea, vomiting, elevated serum amylase and lipase levels) and prompt initiation of appropriate supportive care, including stopping all oral intake.

Didanosine, stavudine and hydroxyurea should be suspended in patients with suspected pancreatitis. Reinstitution of stavudine after a diagnosis of confirmed pancreatitis should be undertaken with caution. Didanosine should be permanently discontinued in patients with confirmed pancreatitis.

The didanosine package insert warns that individuals with risk factors for pancreatitis should use didanosine with extreme caution and only if clearly indicated.

Some of the known risk factors for pancreatitis include:

- history of pancreatitis
- ongoing alcohol abuse
- morbid obesity
- hypertriglyceridemia
- cholelithiasis
- endoscopic retrograde cholangiopancreatography (ERCP)
- other medications known to cause pancreatitis (e.g., pentamidine)
- medications known or thought to increase exposure to didanosine (e.g. hydroxyurea, allopurinol)

In addition, patients with advanced HIV infection are at increased risk for pancreatitis and should be followed closely. When treatment with life-sustaining drugs known to cause pancreatitis is required, suspension of didanosine therapy is recommended.

## REVISED WARNING

Please see enclosed full prescribing information for didanosine, including the revised boxed warning shown below, for additional information and warnings about pancreatitis and other risks associated with the recommended use of didanosine.

The revised boxed warning of the approved product labeling for didanosine is:

WARNING
FATAL AND NONFATAL PANCREATITIS HAS OCCURRED DURING THERAPY WITH VIDEX USED ALONE OR IN COMBINATION REGIMENS IN BOTH TREATMENT-NAÏVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION. VIDEX SHOULD BE SUSPENDED IN PATIENTS WITH SUSPECTED PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS (SEE WARNINGS).

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 AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

Although pancreatitis is described in the didanosine package insert, BMS and FDA request that all cases of pancreatitis occurring in patients treated with didanosine be reported to Bristol-Myers Squibb at 1-800-426-7644 and the FDA via the MEDWATCH by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, by mail at MEDWATCH HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857, or on the MEDWATCH web site at www.FDA.gov/medwatch.

We appreciate this opportunity to be of service to you in the care of your patients. Additional information is available by contacting our Medical Information Department at 1-800-426-7644.

Sincerely,

Michelle Daniels

Michelle Daniels , M.D.
Director, Medical Information
Bristol-Myers Squibb Oncology/Immunology