Bristol-Myers Squibb

February 2007

Re: Important Information Regarding BARACLUDE® (entecavir) in Patients Co-infected with HIV and HBV

Dear Health Care Provider,

Bristol-Myers Squibb is writing to inform you that the company has received a case report in which the selection of a human immunodeficiency virus (HIV) variant containing the M184V resistance substitution was documented during BARACLUDE treatment for chronic hepatitis B virus (HBV) infection in an HIV/HBV co-infected patient who was not simultaneously receiving highly active antiretroviral therapy (HAART). Current treatment guidelines[1-2] recommend BARACLUDE as an option for treatment of HBV in the HIV/HBV co-infected adult patient who does not qualify for HAART; however, in light of the newly-reported case history provided below, BMS advises caution if BARACLUDE is used in this setting.

- BARACLUDE has not been evaluated in HIV/HBV co-infected patients not simultaneously receiving effective HIV treatment.
- When considering therapy with BARACLUDE in an HIV/HBV co-infected patient not receiving HAART, the risk of developing HIV resistance cannot be excluded based on current information.
- Caution is advised if BARACLUDE is used in this setting.

Details of the newly-reported case history are provided below:

- A 31-year-old HIV/HBV co-infected male received combination zidovudine, lamivudine, and nevirapine for less than 1 year in 2000. HAART was discontinued and the patient remained clinically stable with respect to his HIV. In early 2006, with a CD4+ of >500 cells/mm^3 and an HIV-1 RNA of approximately 35,000 copies/mL, BARACLUDE monotherapy was initiated for the treatment of HBV. Within 2 months, the HBV DNA decreased by approximately 5.5 $\log_{10}$ IU/mL, and the HIV RNA decreased to approximately 2,000 copies/mL, subsequently remaining below baseline levels. HIV resistance testing at the start of BARACLUDE therapy did not show resistance, but the M184V substitution was detected following 6 months of therapy with BARACLUDE.

This patient is one of three HIV/HBV co-infected patients not receiving HAART in whom a 1-$\log_{10}$ reduction in HIV RNA has been noted while receiving BARACLUDE as treatment for chronic HBV infection.

Bristol-Myers Squibb has assessed the activity of BARACLUDE against HIV-1 *in vitro*: the EC_{50} for laboratory strains NL4-3, BRU and LAI was >1 µM in cell culture assays.[3]
In addition, BMS has evaluated the use of BARACLUDE 1 mg in the HIV/HBV co-infected population that was receiving simultaneous HAART. These data were from a single randomized, double-blind, placebo-controlled evaluation of the activity of BARACLUDE in 68 HIV/HBV co-infected patients who entered the study with stable HIV-1 RNA <400 copies/mL (mean CD4+ count of 511 cells/mm^3). Patients continued their lamivudine-containing HAART regimen (lamivudine dose 300 mg/day) and were assigned to add either BARACLUDE 1 mg once daily (51 patients) or placebo

(17 patients) for 24 weeks followed by an open-label phase for an additional 24 weeks where all patients received BARACLUDE (entecavir). At Week 24, BARACLUDE-treated patients had a mean reduction in HBV DNA of -3.65 $\log_{10}$ copies/mL compared with an increase of 0.11 $\log_{10}$ copies/mL in the placebo arm. In this setting, no difference in HIV RNA or CD4+ was noted between the BARACLUDE and placebo treatment groups.[4,5]

Bristol-Myers Squibb has collaborated closely with the U.S. Food and Drug Administration on this issue, and the following changes to the package insert are in process of being made:

Under section MICROBIOLOGY/ Antiviral Activity:
"The EC_{50} value of entecavir against human immunodeficiency virus (HIV) type 1 laboratory strains NL4-3, BRU, and LAI was >1 μM in cell culture assays."

Under section INDICATIONS AND USAGE/ Description of Clinical Studies/ *Special Populations*:
"BARACLUDE has not been evaluated in HIV/HBV co-infected patients who were not simultaneously receiving effective HIV treatment."

The revised package insert will be available on www.baraclude.com. If you have any questions about this new information or require additional medical information, please contact Bristol-Myers Squibb at 1-800-321-1335.

If you have had a patient who experienced an adverse event following, or coincident with the use of BARACLUDE, please contact Bristol-Myers Squibb at 1-800-321-1335 or the FDA MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, or by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787).

Please refer to the accompanying Important Information about BARACLUDE and the enclosed BARACLUDE Full Prescribing Information, including **boxed WARNINGS**.

Sincerely,

Freda C. Lewis-Hall, M.D.
Senior Vice President, US Medical Affairs
Bristol-Myers Squibb

Enclosure: BARACLUDE® (entecavir) Package Insert

REFERENCES

1. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 10, 2006. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed Feb. 5, 2007.

2. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology*. 2007;45:507-539.

3. Innaimo SF, Seifer M, Bisacchi GS, et al. Identification of BMS-200475 as a potent and selective inhibitor of hepatitis B virus. *Antimicrob Agents Chemother*. 1997;41:1444-1448.

4. BARACLUDE® (entecavir) Full Prescribing Information, Bristol-Myers Squibb Company, Princeton, New Jersey.

5. Pessoa MG, Gazzard B, Huang A, et al. Entecavir in HIV/HBV co-infected patients: safety and efficacy in a Phase 2 study (ETV-038). *12th Conference on Retroviruses and Opportunistic Infections*; February 22–25, 2005; Boston, MA. Oral Presentation #123.

IMPORTANT INFORMATION ABOUT BARACLUDE® (entecavir) 0.5 mg/1 mg TABLETS:

INDICATION:

BARACLUDE (entecavir) is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

This indication is based on histologic, virologic, biochemical, and serologic responses after one year of treatment in nucleoside-naïve and lamivudine-resistant adult patients with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease, and on more limited data in adult patients with HIV/HBV co-infection who have received prior lamivudine therapy.

IMPORTANT SAFETY INFORMATION:

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals.**

- **Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including BARACLUDE. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted.**

- Dosage adjustment of BARACLUDE is recommended for patients with a creatinine clearance <50 mL/min, patients with age-related decreases in renal function, and those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

- Since entecavir is primarily eliminated by the kidneys, coadministration of BARACLUDE with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the coadministered drug.

- The safety and efficacy of BARACLUDE in liver transplant recipients are unknown. Renal function must be carefully monitored both before and during treatment with BARACLUDE in a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus.

- Patients should be advised that treatment with BARACLUDE has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination.

- There are no adequate and well-controlled studies of BARACLUDE administered to pregnant women. BARACLUDE should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits. There are no studies on the effect of BARACLUDE on transmission of HBV from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition

of HBV. Women should be instructed not to breast-feed if they are taking BARACLUDE® (entecavir).

- Safety and effectiveness of BARACLUDE in pediatric patients below the age of 16 years have not been established.

The most common adverse events of moderate to severe intensity among patients treated with BARACLUDE in clinical trials included: headache (4%), fatigue (3%), diarrhea (1%), and dyspepsia (1%).

The recommended dose of BARACLUDE is 0.5 mg once daily in nucleoside-naïve adults, and 1 mg once daily in lamivudine-refractory adults. BARACLUDE should be administered on an empty stomach (at least 2 hours after a meal and at least 2 hours before the next meal). The optimal duration of treatment with BARACLUDE for patients with chronic hepatitis B infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown.

Please see enclosed Full Prescribing Information, including **boxed WARNINGS**.