Bristol-Myers Squibb

August 2007

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Bristol-Myers Squibb would like to inform you that therapy with BARACLUDE® (entecavir) is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART) due to the potential for the development of HIV (human immunodeficiency virus) resistance.

Accordingly, the BARACLUDE Full Prescribing Information has been updated to include the following information in the **boxed WARNINGS**[1]:

"Limited clinical experience suggests there is a potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if BARACLUDE is used to treat chronic hepatitis B virus infection in patients with HIV infection that is not being treated. Therapy with BARACLUDE is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART). See WARNINGS: Co-infection with HIV."

In addition, the **MICROBIOLOGY** section of the BARACLUDE Full Prescribing Information has been revised to include the following additional information:

Antiviral Activity against HIV
"A comprehensive analysis of the inhibitory activity of entecavir against a panel of laboratory and clinical human immunodeficiency virus type 1 (HIV-1) isolates using a variety of cells and assay conditions yielded EC_{50} values ranging from 0.026 to >10 μM; the lower EC_{50} values were observed when decreased levels of virus were used in the assay. In cell culture, entecavir selected for an M184I substitution in HIV reverse transcriptase at micromolar concentrations, confirming inhibitory pressure at high entecavir concentrations. HIV variants containing the M184V substitution showed loss of susceptibility to entecavir."

Consistent with clinical practice guidelines for chronic hepatitis B management,[2,3] the **WARNINGS** section of the BARACLUDE Full Prescribing Information has been updated with the following information:

"*Before initiating BARACLUDE therapy, HIV antibody testing should be offered to all patients. BARACLUDE has not been studied as a treatment for HIV infection and is not recommended for this use."*

Other changes in the **WARNINGS** and **PRECAUTIONS** sections and **PATIENT INFORMATION** have been made consistent with the information described above. Please refer to the enclosed BARACLUDE Full Prescribing Information, including **boxed WARNINGS**, for more information.

Bristol-Myers Squibb remains committed to providing you the most current and accurate information available for our products.

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 (entecavir), 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

BARACLUDE is a registered trademark of Bristol-Myers Squibb Company.

Enclosure: BARACLUDE Full Prescribing Information

REFERENCES

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

2. Lok AS, McMahon BJ. AASLD practice guidelines: chronic hepatitis B. *Hepatology* 2007;45:507-39.

3. Department of Health and Human Services. Supplement to the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. April 30, 2007. Available at: http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&Search=Off&GuidelineID=7&ClassID=1. Accessed June 27, 2007.

Indication and Important Safety Information about BARACLUDE® (entecavir) Tablets

INDICATION:
BARACLUDE 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 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.**

- **Limited clinical experience suggests there is a potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if BARACLUDE is used to treat chronic hepatitis B virus infection in patients with HIV infection that is not being treated. Therapy with BARACLUDE is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART).** Before initiating BARACLUDE therapy, HIV antibody testing should be offered to all patients.

- BARACLUDE has not been studied as a treatment for HIV infection and is not recommended for this use.

- 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 (entecavir) 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.

- 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**.