U.S. Food and Drug Administration Approves BARACLUDE® (entecavir) as a Treatment for Chronic Hepatitis B Patients with Evidence of Decompensated Liver Disease

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Viral load reduction at 48 weeks in difficult-to-treat chronic hepatitis B patient population

At 48 weeks, 57 percent (57/100) of patients treated with BARACLUDE achieved an undetectable viral load compared to 20 percent (18/91) of patients who received adefovir.

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) announced today that the U.S. Food and Drug Administration (FDA) has approved the supplemental New Drug Application (sNDA) of BARACLUDE for the treatment of chronic hepatitis B (CHB) in adult patients with decompensated liver disease. BARACLUDE is indicated for the treatment of CHB 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 new approval is based on virologic, biochemical, serologic, and safety data from a controlled, ongoing, open-label Phase IIIb study (ETV-048). This study compares BARACLUDE (1 mg once daily) to adefovir (10 mg once daily) in CHB patients with decompensated liver disease. Data demonstrated that BARACLUDE was effective in this patient population. BARACLUDE showed greater viral suppression compared to adefovir at 48 weeks following treatment initiation.

"This additional indication for BARACLUDE is important news as it is now proven to be an effective treatment option for physicians to help in managing chronic hepatitis B patients with decompensated liver disease,” said Dr. Naoky Tsai, MD, professor of medicine at the John A. Burns School of Medicine at the University of Hawaii, Honolulu.

Decompensated liver disease refers to failure of the liver to maintain adequate function, often due to severe scarring of the liver. Chronic hepatitis B infection is commonly associated with chronic liver inflammation and can lead to decompensated liver function.

ETV-048 Study

A key study endpoint of ETV-048 was the proportion of subjects with undetectable HBV DNA viral load (<300 copies/mL). A greater proportion of patients on BARACLUDE (entecavir) achieved an undetectable viral load compared to patients on adefovir at 48 weeks: 57 percent (57/100) versus 20 percent (18/91), respectively.

In the BARACLUDE arm, the most common adverse reactions of any severity, regardless of causality, occurring through Week 48 were peripheral edema (16 percent), ascites (15 percent), pyrexia (14 percent), hepatic encephalopathy (10 percent), and upper respiratory infection (10 percent).

Additional ETV-048 Study Outcomes

Among patients with baseline abnormal alanine aminotransferase (ALT), a higher proportion of BARACLUDE-treated patients achieved ALT normalization (≤1 x Upper Limit of Normal) at Week 48 [63 percent (49/78)] compared with adefovir-treated patients [46 percent (33/71)].

One secondary study endpoint was the improvement in Child-Turcotte-Pugh (CTP) Score, which scores patients on the severity of chronic liver disease. Within this study, 61 percent (61/100) of patients on BARACLUDE and 67 percent (61/91) of patients on adefovir had an improvement or no worsening of the CTP Score at Week 48 compared to their baseline values.

Additionally, at Week 48 hepatitis B surface antigen (HBsAg) loss was observed in 5 percent (5/100) of BARACLUDE-treated patients and in none of the adefovir-treated patients (0/91).
**Study ETV-048 Design**

Study ETV-048 is a randomized, open-label Phase IIIb study of BARACLUDE compared to adefovir in HBeAg-positive or HBeAg-negative patients with chronic hepatitis B infection and evidence of hepatic decompensation (CTP score ≥ 7 with no upper limit). Subjects were either HBV-treatment naïve or previously treated predominantly with lamivudine or interferon-alpha.

Patients were randomized to receive BARACLUDE 1 mg once daily (n=100) or adefovir 10 mg once daily (n=91). At baseline, subjects had a mean serum HBV DNA by PCR of 7.83 log_{10} copies/mL and mean ALT level of 100 U/L; 54% of subjects were HBeAg-positive; 35% had genotypic evidence of lamivudine resistance. The baseline mean CTP score was 8.6.

**About BARACLUDE (entecavir)**

BARACLUDE, a nucleoside analogue discovered at Bristol-Myers Squibb, was first approved in March 2005 for use in adult chronic hepatitis B patients with compensated liver disease. The initial approval was based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment-naïve and lamivudine-resistant adult subjects with HBeAg-positive or HBeAg-negative CHB infection and compensated liver disease.

**About Chronic Hepatitis B**

Chronic hepatitis B is a serious viral infection that causes damage to the liver. An estimated 1.25 million Americans are chronically infected with hepatitis B, and over half are of Asian descent.

**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.

The following points should be considered when initiating BARACLUDE:

- This indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment-naïve and lamivudine-resistant adult subjects with HBeAg-positive or HBeAg-negative chronic HBV infection and compensated liver disease.

- Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease.

- Virologic, biochemical, serologic, and safety data are available for a limited number of adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy.

**IMPORTANT SAFETY INFORMATION:**

**Warnings: Severe Acute Exacerbations of Hepatitis B, Patients Co-infected with HIV and HBV, Lactic Acidosis, and Hepatomegaly**

- Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including BARACLUDE (entecavir). 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 HBV 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.

- 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. Baraclude should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

**Drug Interactions**

BARACLUDE (entecavir) is primarily eliminated by the kidneys, therefore 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. Patients should be monitored closely when receiving BARACLUDE with other renally eliminated drugs.

**Pregnancy and Nursing Mothers**

- There are no adequate and well-controlled studies of BARACLUDE in 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.
It is not known whether BARACLUDE is excreted into human milk, however many drugs are excreted into breast milk. Due to the potential for serious reactions in nursing infants from BARACLUDE, risks and benefits should be considered when deciding whether to discontinue breastfeeding or discontinue BARACLUDE in nursing women.

**Pediatric Use**

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

**Renal Impairment**

- Dosage adjustment of BARACLUDE is recommended for patients with a creatinine clearance <50 mL/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).
- The safety and efficacy of BARACLUDE (entecavir) 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.

**Adverse Reactions**

- In clinical trials in patients with compensated liver disease, the most common (≥3%) adverse reactions of any severity with at least a possible relation to study drug for BARACLUDE-treated subjects were headache, fatigue, dizziness, and nausea. In these trials, the most common adverse reactions of moderate to severe intensity (grades 2-4) were diarrhea, dyspepsia, nausea, vomiting, fatigue, headache, dizziness, somnolence, and insomnia.
- In the decompensated liver disease trial, the most common adverse reactions of any severity among patients treated with BARACLUDE, regardless of causality, included: peripheral edema (16%), ascites (15%), pyrexia (14%), hepatic encephalopathy (10%), and upper respiratory infection (10%). In this trial, 18% (18/102) of BARACLUDE patients and 20% (18/89) of adefovir patients died during the first 48 weeks of therapy. The majority of those deaths were due to liver related causes.

**Dosage and Administration**

The recommended dose of BARACLUDE Tablets:

- In nucleoside-naïve adults and adolescents (16+ yrs) with compensated liver disease is 0.5 mg once daily
- In adults and adolescents (16+ yrs) with compensated liver disease, and refractory to lamivudine or with known lamivudine or telbivudine resistance mutations (rtM204I/V with or without rtL180M, rtL80I/V, or rtV173L) is 1 mg once daily
- In adults with decompensated liver disease is 1 mg once daily

BARACLUDE should be administered on an empty stomach (at least 2 hours after a meal and at least 2 hours before the next meal).

**Additional Information**

BARACLUDE (entecavir) is not a cure for HBV. The optimal duration of treatment with BARACLUDE for patients with chronic HBV infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown.

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.

Please see Full Prescribing Information, including boxed WARNINGS available at www.BARACLUDE.com.

**About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit http://www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

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**BARACLUDE** (entecavir) is a registered trademark of Bristol-Myers Squibb.

**References**


**Language:**

English

**Contact:**

Bristol-Myers Squibb Company