Entecavir Approved for Chronic Hepatitis B

BY ELIZABETH MECHCATIE
Senior Writer

GAITHERSBURG, MD. — Entecavir, an oral antiviral drug that has several advantages over currently available treatments for chronic hepatitis B, was approved recently by the Food and Drug Administration.

The approval came subsequent to the unanimous recommendation of all 18 members of the FDA's Antiviral Drugs Advisory Committee who agreed that the risk-benefit appraisal of entecavir supported its approval for treating chronic hepatitis B virus (HBV) infections in adults.

Despite concerns about a theoretical risk of malignancies, the panel voted in favor of approval, citing the very real risk of hepatocellular carcinoma associated with chronic HBV, safety and effectiveness data in 48-week trials of more than 1,000 patients who were either treatment naïve or refractory to lamivudine, and the lack of significant evidence of resistance to date.

There is "no question" that entecavir is very effective at reducing viral load, said Leonard Seeff, M.D., senior scientist for hepatitis research at the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md., a member of the panel. "We need other treatments, and this drug has advantages that others don't—namely, at least at this point, a lower rate of mutant strains developing and no nephrotoxicity."

Kenneth Sherman, M.D., director of the hepatology and liver transplant medicine section at the University of Cincinnati, added that "as a hepatologist, I think this drug will add significantly to the tools we have available to treat patients with liver disease."

The drug's manufacturer, Bristol-Myers Squibb (BMS), has agreed to conduct a large postmarketing study to determine whether the increased risk of lung tumors and other malignancies seen in rodents would occur in humans, and whether resistant strains would develop with a longer duration of treatment. The multinational trial would aim to enroll 12,500 patients worldwide, randomize them to entecavir or another HBV drug treatment, and follow them for malignancies and progression of liver disease for 5-8 years, according to BMS.

But the panel was concerned that the company could have problems enrolling enough patients in the trial, because entecavir was shown to be more effective than lamivudine in trials. Panel members also suggested that patients may have to be followed for longer periods.

BMS will market entecavir under the trade name Baraclude. Entecavir is a nucleoside analogue that is a potent, selective inhibitor of HBV replication. Currently available treatments for chronic HBV include interferon, approved in 1992, which is administered subcutaneously and is limited by its side effect profile. The first effective oral treatment for HBV, lamivudine (Epivir), a nucleoside analogue, was approved in 1998, but its usefulness is limited by the emergence of resistant strains after short durations of treatment.

Adefovir dipivoxil (Hepsera), a nucleotide analogue approved in 2002, is active against lamivudine-resistant virus, but can cause nephrotoxicity, which may limit its use in some populations.

At the meeting, BMS presented the results of clinical trials, including three phase III studies comparing entecavir with lamivudine in more than 1,500 patients with chronic HBV infections and active liver inflammation, including HBeAg-negative and HBeAg-positive patients who had not been treated with a nucleoside, and HBeAg-positive patients who were refractory to lamivudine. The patients in the trials did not have HIV.

In all three groups of patients, a significantly greater proportion of those treated with entecavir than of those treated with lamivudine met the primary end point, histologic improvement in liver biopsy after 48 weeks of treatment. Among the treatment-naïve patients, 70%-72% of those on entecavir met this end point vs. 61%-62% of those on lamivudine. Among lamivudine-refractory patients, 55% met this end point, vs. 28% of those who remained on lamivudine.

The safety profiles and malignancy rates were comparable in the entecavir and lamivudine-treated groups, according to the company.

Entecavir also has a favorable resistance profile compared with lamivudine, according to BMS:

Among entecavir-treated patients, viral resistance was not detected in any treatment-naïve patients at 48 weeks and was low among lamivudine-refractory patients (7%, leading to virologic rebound in 2%).

Hepatitis B affects about 400 million people worldwide, with about 1.25 million in the United States, and is the most common cause of cirrhosis and hepatocellular carcinoma, according to the FDA. ■

CLINICAL GUIDELINES FOR FAMILY PHYSICIANS

Chronic Hepatitis B Infection

BY NEIL S. SKOLNIK, M.D., AND JANE KONG, M.D.

Chronic hepatitis B affects roughly 350 million people worldwide. Another 1.25 million U.S. residents are carriers (defined as hepatitis B surface antigen–positive for more than 6 months). Of those, 15%-40% will develop serious sequelae from chronic hepatitis B during their lifetime. Guidelines from the American Association for the Study of Liver Diseases discuss diagnosis, treatment, and prevention for patients with chronic hepatitis B virus.

Diagnosis and Screening

To be diagnosed with chronic hepatitis B virus (HBV), a patient must be hepatitis B surface antigen (HbsAg)–positive for more than 6 months; have more than 105 copies/mL of serum HBV DNA; have persistent or intermittent elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels; and have chronic hepatitis on liver biopsy.

Guidelines are most useful when they are available at the point of care. A concise yet complete handheld computer version of this guideline is available for download, compliments of FAMILY PRACTICE NEWS, *at www.redi-reference.com.*

Screening should be done on those born in hyperendemic areas, men who have sex with men, intravenous drug users, dialysis patients, HIV-infected individuals, pregnant women, and household contacts and sexual partners of patients with HBV. Serum should be tested for HBsAg and the hepatitis B surface antibody (anti-HBs).

Seronegative patients should be vaccinated and HbsAg-positive patients should be evaluated for liver disease activity and the need for antiviral therapy. Patients with chronic HBV should be vaccinated against hepatitis A with two doses given 6-18 months apart. Prior to initiating treatment, patients should be monitored for 3-6 months for spontaneous seroconversion to hepatitis B e antibody (anti-Hbe).

Once a patient has seroconverted from hepatitis B e antigen (HbeAg) to anti-HBe, most will enter an inactive carrier state in which DNA levels drop to below detection, ALT normalizes, and necroinflammation decreases. In patients who do not seroconvert, a liver biopsy should be performed to assess liver damage and to rule out other etiologies for liver disease. Patients in the inactive HbsAg carrier state should have liver function tests every 6-12 months; up to 30% may develop reactivation of hepatitis B despite long periods of quiescence.

To prevent HBV transmission, carriers should be counseled on sexual or perinatal transmission or inadvertent transmission via blood spills. Newborns of infected mothers should receive hepatitis B immunoglobulin (HBIG) and HBV vaccine at birth, then complete the recommended vaccination series. Those with persistent risk for HBV infection (infants of HBsAg-positive mothers, health care workers, dialysis patients, and sexual partners of carriers) should be tested for response to vaccination. Infants of carrier mothers should have postvaccination testing done at 3-9 months after the last dose; others should be tested 1-2 months after the last dose. Chronic hemodialysis patients who are vaccine responders should be tested annually.

Periodic screening with both -fetoprotein and ultrasonography should be done for carriers at high risk for hepatocellular carcinoma (HCC), such as men aged 45 years and older, patients with cirrhosis, or patients with family history of HCC. Periodic screening with -fetoprotein also should be considered for carriers from endemic areas.

Treatment

Treatment recommendations for HBeAg-positive patients include:

► For ALT greater than twice the normal level or for patients with moderate to severe hepatitis on biopsy, consider treatment with interferon- (IFN-), lamivudine, or adefovir. All have similar efficacy.

► If ALT is persistently normal or minimally elevated (less than twice the normal level), do not start treatment unless liver biopsy (optional) shows moderate or severe necroinflammation.

► For children, consider treatment if ALT is greater than twice the normal level for longer than 6 months. Both IFN- and lamivudine are approved for children. Consider treating HBe-negative patients who have chronic HBV with IFN- , lamivudine, or adefovir. IFN- or adefovir are preferred if long-term treatment is needed. IFN- is administered subcutaneously for 16 weeks in HbeAg-positive and for 12 months in HBeAg-negative patients. Lamivudine and adefovir are administered orally for at least 1 year in HbeAg-positive patients and longer in HbeAg-negative patients.

Patients who fail IFN- may be treated again with lamivudine or adefovir if they fulfill the criteria above. Adefovir should be given to those who develop breakthrough infection while on lamivudine. Patients with compensated cirrhosis should be treated with lamivudine or adefovir to avoid hepatic decompensation from flares of hepatitis associated with IFN- . Lamivudine should be considered for patients with decompensated cirrhosis. Although adefovir has not been evaluated as a primary agent in these patients, it may be used as an alternative, in which case renal function (BUN/creatinine) should be monitored every 1-3 months. IFN- should not be used in patients with decompensated cirrhosis. Treatment is not indicated for the inactive HBsAg carrier state.

DR. SKOLNIK is associate director of the family medicine residency program at Abington (Pa.) Memorial Hospital. He is also the coauthor of the "Redi-Reference Clinical Guidelines" handbook for handheld computers. DR. KONG *is a second-year resident at the hospital.*