Entecavir (Baraclude) for the Treatment of Chronic Hepatitis B Virus (HBV) Infection

Nino Marzella, BS, PharmD

INTRODUCTION

Approximately two billion people have serologic evidence of hepatitis B virus (HBV) infection, and almost 350 million individuals worldwide are chronic carriers of the virus. In the U.S. alone, approximately 1 million individuals have chronic HBV infection.

HBV infection remains endemic in many areas throughout the world, including Africa, Eastern Europe, Central Asia, China, Southeast Asia, the Pacific Islands, the Middle East, and the Amazon basin of South America. Yet certain developing countries continue to have only limited resources and lack appropriate treatment regimens against this infection. Consequently, health care costs continue to escalate with diminishing quality of life in patients afflicted with this chronic, debilitating disease.

HBV belongs to the family of hepadnaviruses and is considered a small, enveloped, partially double-stranded DNA virus. Following viral exposure, the HBV incubation period may vary anywhere from six weeks to six months.

HBV can be acquired in several ways (e.g., sexual contact, instruments, percutaneous or mucosal exposure to blood or body fluids of an infected person not immune to HBV). Table 1 lists the various modes of transmission.

Higher concentrations of HBV have been found in the blood, in comparison with lower concentrations identified in other body fluids (e.g., vaginal secretions, semen, sweat, and tears). Adults 18 to 39 years of age tend to be at high risk for the development of HBV infection because of specific behavioral practices.

The diagnosis of HBV infection is made on the basis of clinical evidence and serologic testing. Serologic markers can indicate when the infection is acute or chronic, whether the person has been immunized, or whether the infection has been resolved. Table 2 lists serologic markers for HBV infection.

Acute cases reveal immunoglobulin M (IgM) antibody–positive against hepatitis B core antigen (IgM anti-HBc). Hepatitis B surface antigen (HBsAg) may be present in either acute or chronic cases of infection. Antibodies to HBsAg (anti-HBsAg) are produced upon resolution of infection or following immunization.

Primary HBV infections can be self-limiting, and they usually resolve. However, HBV can develop into a persistent form, progressing to a chronic state, which can lead to serious sequelae, including chronic liver disease, hepatic decompensation, cirrhosis, hepatocellular carcinoma, extrahepatic manifestations, and death. Table 3 lists the clinical manifestations of HBV infection (see page 315).

Three regimens have been approved by the Food and Drug Administration (FDA) for the treatment of chronic HBV infection: interferon alfa-2b (Intron A, Schering), lamivudine (Epivir-HBV, 3TC, GlaxoSmithKline), and adefovir dipivoxil (Hepsera, Gilead). Table 4 compares the current regimens (see page 316).

Adverse drug events (ADEs) and viral resistance are vital components when one is differentiating between the various regimens. Additional considerations include an evaluation and screening of possible co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis D virus (HDV), illnesses that are increasing drastically, thus warranting alternative treatment approaches.

In March 2005, the FDA approved entecavir (Baraclude, Bristol-Myers Squibb), a nucleoside analogue that demonstrates selective activity against HBV. As with any treatment against chronic HBV, the goals of therapy include decreasing active liver inflammation by correcting serologic parameters and liver enzymes in hepatitis, stopping the progression of hepatitis to cirrhosis, preventing hepatocellular carcinoma, and improving the patient’s quality of life by prolonging survival.

INDICATION AND USAGE

Entecavir is indicated for adults with chronic HBV who have evidence of viral replication and persistent elevations in serum aminotransferases (ALT, AST) or active disease based on histologic findings. Entecavir is approved for patients with HBeAg-positive, HBeAg-negative, and lamivudine-resistant infection.

CLINICAL PHARMACOLOGY

Entecavir is an oral analogue of 2′-deoxyguanosine. Following phosphorylation to its active triphosphate form via enzymatic pathways, entecavir is a potent inhibitor of HBV replication. Inhibition of HBV viral production occurs through three mechanisms:

- priming of HBV-DNA polymerase
- reverse transcription of the negative strand from the pre-genomic RNA
- synthesis of the positive DNA strand

Disclosure: Dr. Marzella has no commercial or industrial relationships to disclose in regard to this article.
Entecavir has been a problem, particularly if one is targeting a sustained viral response against HBV infection. So far with entecavir, cross-resistance with HBV nucleoside analogues has been observed. Resistance emerges in 14% to 32% of HBV-infected patients who have received lamivudine for one year, and this figure increases to approximately 70% at five years.

Adefovir dipivoxil–resistant strains emerge at a lower rate (from 4% at three years). In cell-based assays, however, entecavir revealed eight-fold to 30-fold less inhibition of replication to HBV containing lamivudine resistance mutations rtL180M and/or rtM204V/I than of wild-type virus. Entecavir also remains susceptible to adefovir-resistant genomes to HBV encoding the rtN236T or rtA181V strain.

In vitro testing has shown that patients who had been considered lamivudine-refractory and who had not responded to entecavir were responsive to adefovir dipivoxil but still retained resistance to lamivudine. In clinical trials of nucleoside-naive patients, entecavir demonstrated no evidence of phenotypic and genotypic changes detected with entecavir-resistant strains. However, lamivudine-refractory patients showed possible evidence of emerging resistance to entecavir by week 48, especially in the presence of lamivudine mutations identified as rtL180M and/or rtM204V/I.

**PHARMACOKINETICS**

In healthy subjects, peak plasma concentrations of entecavir occur between 0.5 and 1.5 hours after oral administration, and steady-state concentrations are observed after six to 10 days. Entecavir has an accumulation half-life of approximately 24 hours, thus allowing for once-daily dosing.

In addition, the bioavailability of oral entecavir tablets is equal to that of the oral solution; thus, the two dosage forms are considered interchangeable.

Entecavir does not appear to be a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) system, and it is not metabolized through either oxidative or acetylation mechanisms. Minor glucoronidative and sulfate conjugates

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**Table 1: Modes of Hepatitis B Virus (HBV) Transmission**

<table>
<thead>
<tr>
<th>Mode</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal transmission</td>
<td>High infection rate among infants born to HBeAg-positive mothers; can be acquired in utero, during birth, or after birth.</td>
</tr>
<tr>
<td>Horizontal transmission</td>
<td>Children may acquire HBV infection via minor cuts on the skin or the mucous membranes of other infected children.</td>
</tr>
<tr>
<td>Sexual transmission</td>
<td>A major mode of transmission, especially with homosexual activity.</td>
</tr>
<tr>
<td>Percutaneous inoculation</td>
<td>Examples include intravenous drug users sharing needles or syringes with infected persons and household contacts sharing toothbrushes and razors. Tattooing, body piercing, and acupuncture have also been associated with HBV transmission.</td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>HBV is the most common blood-borne virus in the health care setting; it can be spread from patient to patient or through contaminated instruments and needlestick accidents.</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>HBV infection has been reported after extrahepatic transplantation.</td>
</tr>
</tbody>
</table>


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**Table 2: Serologic Markers for Hepatitis B Virus (HBV) Infection**

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>IgM Anti-HBc</th>
<th>IgG Anti-HBc</th>
<th>HBeAg</th>
<th>Anti-HBe</th>
<th>HBV–DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–/+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>HBeAg−</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Immunized</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Resolved infection</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

anti-HB = hepatitis B envelope antibody; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B envelope antigen; HBsAg = hepatitis B surface antigen; Ig = immunoglobulin; IgM anti-HBc = hepatitis B core antibody IgM; IgG anti-HBc = hepatitis B core antibody IgG.

Chronic Infection

- Fatigue
- Anorexia
- Nausea and vomiting
- Myalgia
- Low-grade fever
- Right upper-quadrant pain
- Elevated ALT/AST, PT
- Jaundice
- Scleral icterus
- Dark urine
- Light-colored stools
- Pruritus
- "Serum sickness-like syndrome" (fever, rash, arthritis)

Chronic phase: Manifestations range from subclinical or anicteric to icteric hepatitis and, in some cases, to fulminating hepatitis.

CLINICAL TRIALS

The FDA’s approval of entecavir was based on clinical trials in which histologic, virologic, biochemical, and serologic responses were observed after one year of treatment. The study population included nucleoside-naive and lamivudine-resistant patients with HBeAg-positive or HBeAg-negative chronic HBV infection with decompensated liver disease.

In terms of co-infection with HBV and HIV, limited data on the safety and efficacy were studied within a small sample population.

Nucleoside-Naive Patients (Studies AI463022 and AI463027)

A multinational, randomized double-blind trial was conducted to evaluate the safety and efficacy of nucleoside-naive, HBeAg-positive patients with chronic hepatitis B. Enrollment consisted of 709 patients after 715 patients were randomly assigned to receive either 0.5 mg of once-daily oral entecavir or 100 mg of once-daily oral lamivudine for 52 weeks. At the baseline evaluation, patients had a mean score of 7.8 on the Knodell Necroinflammatory Scale, a mean serum HBV-DNA load of 9.66 log_{10} copies/ml, and a mean ALT concentration of 142 U/L.

In summary, both trials found entecavir superior to lamivudine based on the primary endpoint, which was observed at 48 weeks. The primary endpoint was defined as histologic improvements of a reduction of two or more points in Knodell Necroinflammatory Scale scores and with no clinical deterioration in Knodell Fibrosis Scale scores.

Secondary endpoints, which included a reduction in viral load and ALT levels, further demonstrated improvements within the entecavir treatment arm. For the HBeAg-positive patients, 72% of those receiving entecavir displayed histologic improvement, compared with 62% of the lamivudine patients at week 48 (P < .05). For the HBeAg-negative patients, 70% of the entecavir patients showed histological improvement, compared with 61% of the lamivudine patients at week 48 (P = .05).

Undetectable HBV–DNA and normalization of ALT values were documented with statistical significance for both HBeAg-positive and HBeAg-negative patients. Undetectable HBV-DNA levels in HBeAg-positive patients were reported in 67% of those receiving entecavir and in 36% of those receiving lamivudine (P = .05); and undetectable HBV–DNA levels in HBeAg-negative patients were reported in 90% of those receiving entecavir and in 72% of those receiving lamivudine (P = .05).

Normalised ALT levels (defined as one times the upper limit of normal or less) were reported in 68% of HBeAg-positive patients receiving entecavir and in 60% of patients receiving lamivudine (P = .05) and in 78% of HBeAg-negative patients receiving entecavir and in 71% of patients taking lamivudine (P = .05).

In summary, both trials found entecavir superior to lamivudine in terms of the primary endpoint (histologic improvement) and in secondary endpoints (reductions in viral load and normalization of ALT values) in each treatment arm.

Lamivudine-Resistant Patients (Study AI463026)

A multinational, randomized, double-blind trial enrolled 286 (of 293) patients with chronic HBV infection who had not of entecavir have been observed in clinical trials.

Entecavir is primarily eliminated, unchanged, by the kidneys; it is cleared by filtration and renal tubular secretion in a non–dose-dependent fashion. Thus, the agent’s half-life is prolonged in renally impaired patients, and the dose should be adjusted according to the degree of impairment.

Table 3 Clinical Manifestations of Hepatitis B Virus (HBV) Infection

<table>
<thead>
<tr>
<th>Acute Infection</th>
<th>Chronic Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatigue</td>
<td>• HBSAg-positive for more than six months</td>
</tr>
<tr>
<td>• Anorexia</td>
<td>• Arthralgia</td>
</tr>
<tr>
<td>• Nausea and vomiting</td>
<td>• Rash</td>
</tr>
<tr>
<td>• Myalgia</td>
<td>• Elevated ALT/AST</td>
</tr>
<tr>
<td>• Low-grade fever</td>
<td>• PT, albumin, and bilirubin typically within normal ranges; however, with progression to cirrhosis, values change significantly</td>
</tr>
<tr>
<td>• Right upper-quadrant pain</td>
<td>• Persistent mild hepatomegaly and splenomegaly may be observed</td>
</tr>
<tr>
<td>• Elevated ALT/AST, PT</td>
<td>• duke on the Knodell Necroinflammatory Scale scores, and with no clinical deterioration in Knodell Fibrosis Scale scores.</td>
</tr>
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</table>

In both trials, entecavir was considered superior to lamivudine based on the primary endpoint, which was observed at 48 weeks. The primary endpoint was defined as histologic improvements of a reduction of two or more points in Knodell Necroinflammatory Scale scores and with no clinical deterioration in Knodell Fibrosis Scale scores.

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Lamivudine-Resistant Patients (Study AI463026)

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### Interferon alfa-2b (Intron-A, Schering)
- Effects on HBV infection only:
  - Immunomodulatory effects
  - Direct antiviral effects
  - Inhibition of viral RNA
  - Pre-genomic packing in core
  - Particles and enhancement
  - Expression of HBsAg on hepatocytes

### Lamivudine (Epivir-HBV, GlaxoSmithKline)
- Analogue of nucleoside cytosine
- Intracellular conversion to 3TC–TP (the active form)
- Incorporation into DNA during replication causes disruption in chain

### Adefovir Dipivoxil (Hepsera, Gilead)
- Nucleotide analogue of adenosine monophosphate
- Phosphorylated to adefovir diphosphate (the active form)
- Inhibits viral DNA

### Adult dose
- Interferon alfa-2b: 5 MU q.d. or 10 MU t.i.w. SQ older than 1 year of age
- Lamivudine: 100 mg PO q.d.
- Adefovir Dipivoxil: Not established

### Pediatric dose
- Interferon alfa-2b: 6 MU/m² t.i.w. (maximum, 10 MU)
- Lamivudine: 3 mg/kg per day (maximum, 100 mg/day)
- Adefovir Dipivoxil: Not established

### Dosage adjustments
- Interferon alfa-2b: None, but use caution in severe renal impairment
- Lamivudine: Renal
- Adefovir Dipivoxil: Renal

### Route
- Interferon alfa-2b: SQ injection
- Lamivudine: Oral
- Adefovir Dipivoxil: Oral

### Adverse events
- Interferon alfa-2b: Multiple effects *
  - Flu-like syndrome; fever, chills, headache, and myalgias (especially when beginning treatment; early onset)
  - Granulocytopenia, thrombocytopenia, anemia
  - Depression, psychosis
  - Anorexia, alopecia
  - Hyperglycemia
  - Hyperlipidemia (TG)
  - SIADH
  - Thyroid dysfunction
- Lamivudine: Well tolerated
  - Headache
  - Fatigue
  - Nausea
  - Abdominal discomfort
- Adefovir Dipivoxil: Well tolerated
  - Nephrotoxicity
  - Hypophosphatemia

### Resistance
- Interferon alfa-2b: None
- Lamivudine: Increasing
- Adefovir Dipivoxil: Less incidence; increasing

### Monitoring
- Interferon alfa-2b: Liver enzymes, HBsAg and HBeAg at end of therapy; three and six months after treatment
- Lamivudine: Liver enzymes, HBV-DNA regularly during therapy and several months after therapy ends
- Adefovir Dipivoxil: Liver enzymes, HBV-DNA, hepatitis antigen and antibody periodically

### Cost
- Interferon alfa-2b: $$$
- Lamivudine: $
- Adefovir Dipivoxil: $$$

* Many precautions for use.

CBC = complete blood count; HBeAg = hepatitis B envelope antigen; HBsAg = hepatitis B surface antigen; MU = million units; q.d. = once daily; SIADH = syndrome of inappropriate antidiuretic hormone (secretion); SQ = subcutaneous; TG = triglycerides; t.i.w. = three times per week; 3TC–TP = lamivudine triphosphate.


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**Table 4 Comparison of Therapies for Patients with Chronic Hepatitis B Virus (HBV) Infection**

<table>
<thead>
<tr>
<th>Effect and mechanism of action</th>
<th>Interferon alfa-2b (Intron-A, Schering)</th>
<th>Lamivudine (Epivir-HBV, GlaxoSmithKline)</th>
<th>Adefovir Dipivoxil (Hepsera, Gilead)</th>
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<tr>
<td></td>
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<td>• Particles and enhancement</td>
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<td>Adult dose</td>
<td>5 MU q.d. or 10 MU t.i.w. SQ older than 1 year of age</td>
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<td>10 mg PO q.d.</td>
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<td>Pediatric dose</td>
<td>6 MU/m² t.i.w. (maximum, 10 MU)</td>
<td>3 mg/kg per day (maximum, 100 mg/day)</td>
<td>Not established</td>
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<tr>
<td>Dosage adjustments</td>
<td>None, but use caution in severe renal impairment</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td>Route</td>
<td>SQ injection</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Adverse events</td>
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<td></td>
<td>• SIADH</td>
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<td></td>
<td>• Thyroid dysfunction</td>
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<tr>
<td>Resistance</td>
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<td>Less incidence; increasing</td>
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<tr>
<td>Monitoring</td>
<td>• Liver enzymes</td>
<td>• Liver enzymes</td>
<td>• Liver enzymes</td>
</tr>
<tr>
<td></td>
<td>• HBsAg and HBeAg at end of therapy; three and six months after treatment</td>
<td>• HBV-DNA regularly during therapy and several months after therapy ends</td>
<td>• Hepatitis B antibody and antigen</td>
</tr>
<tr>
<td></td>
<td>• HBV-DNA in selected patients</td>
<td>• Check hepatitis antigen and antibody periodically</td>
<td>• Quality-of-life assessment</td>
</tr>
<tr>
<td></td>
<td>• Liver biopsy when applicable</td>
<td>• Body weight, vital signs, chest x-ray, appetite</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• CBC and platelets</td>
<td>• Quality-of-life assessment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Quality-of-life assessment</td>
<td></td>
<td></td>
</tr>
</tbody>
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responded to lamivudine. A switch to entecavir provided beneficial results in overall histologic, virologic, and biochemical responses compared with continuous lamivudine therapy. Patients either continued with oral lamivudine 100 mg daily or began a regimen of oral entecavir 1 mg daily, after a washout period, for 52 weeks. At 48 weeks, more histologic improvements were seen with entecavir (55%) than with lamivudine (28%) (P = .01).

The Knodell Necroinflammatory Scale was used to assess improvement. At 48 weeks, Ishak Fibrosis Scale scores were also significantly improved in the entecavir patients (34%) compared with the lamivudine group (16%) (P = .01). When undetectable HBV–DNA was evaluated, it was determined that patients with fewer than 300 copies/ml were taking entecavir (19%), in contrast to those in the lamivudine group (1%) (P = .0001). The mean change in HBV–DNA was also statistically significant (P = .0001).

The return of liver enzyme values (i.e., ALT) to normal was superior with entecavir (61%) than with lamivudine (15%) (P = .0001). Overall, entecavir was effective for lamivudine-refractory patients with chronic HBV infection.

### Patients with HIV Infection

(Study AI463038)

This double-blind placebo-controlled trial evaluated patients experiencing a recurrence of HBV infection in addition to being co-infected with HIV. All enrolled patients (n = 198) were receiving HAART, including a standard regimen of lamivudine at 300 mg daily.

The patients were randomly assigned to receive entecavir 1 mg orally or placebo for 24 weeks, followed by an open-label phase for an additional 24 weeks, the point at which all patients could receive entecavir. At the start of the study, 99% of the patients were HBeAg-positive.

The mean baseline serum HBV–DNA concentration was recorded at 71.5 U/L. At 24 weeks, undetectable HBV–DNA was reported as 6% in the entecavir patients, in contrast to 0% in the placebo group. The mean change in HBV–DNA, however, did show statistical significance between entecavir (reported as −3.65 copies/ml) and placebo (reported as +0.11 copies/ml) (P = .001).

Normalized ALT levels occurred at a rate of 34% with entecavir and at a rate of 8% with placebo, although no statistical analysis was reported.

### ADVERSE DRUG EVENTS

The most commonly reported adverse drug events (ADEs) associated with entecavir were headache, fatigue, dizziness, nausea, insomnia, and somnolence. In clinical trials, the incidence of these ADEs was comparable to those reported in patients using lamivudine (Epivir HBV).

Lactic acidosis and severe hepatomegaly have been reported with nucleoside analogues such as entecavir. Some patients have also experienced exacerbations of HBV infection, which occurred during entecavir therapy and upon discontinuation of entecavir.

### PREGNANCY

Entecavir is classified as a pregnancy category C agent.

### DRUG INTERACTIONS

Because entecavir is eliminated primarily through the kidneys, vigilant clinical monitoring and dosage adjustments should be considered if other renally eliminated agents are being coadministered. The administration of entecavir with nucleoside reverse transcriptase inhibitors (NRTIs) was favorable and did not demonstrate a decrease in antiviral efficacy in either treatment regimen.

In vitro testing was performed with additional agents such as abacavir (Zidovudine, GlaxoSmithKline), didanosine (Videx, Bristol-Myers Squibb), lamivudine, stavudine (Zerit, Bristol-Myers Squibb), tenofovir (Viread, Gilead), and zidovudine (Retrovir, AZT, GlaxoSmithKline). No significant antagonistic properties were apparent at wide range concentrations. Studies of specific drug interactions with the use of entecavir are under way.

### CONTRAINDICATIONS

Entecavir is contraindicated in patients with a known hypersensitivity to any component of the product.

### PRECAUTIONS AND WARNINGS

Severe acute exacerbations of hepatitis B flare-ups have been reported upon abrupt discontinuation of entecavir therapy. As a result, when discontinuation of HBV therapy is appropriate, close clinical and laboratory monitoring is essential and should continue for several months.

The administration of nucleoside analogues alone or in combination with antiretroviral agents has led to the development of lactic acidosis and severe hepatomegaly with steatosis. Although entecavir has been found safe and efficacious in patients with hepatic impairment, liver transplant recipients should be advised that the safety and efficacy of...
Drug Forecast

this drug are not confirmed.

Dosage adjustments are recommended in patients with renal insufficiency (Table 5).

**DOSAGE AND ADMINISTRATION**

Entecavir is indicated for adults and adolescents 16 years of age or older with chronic HBV infection. The safety and efficacy with entecavir in children have not been established, and the drug is not recommended for children at this time.

Patients with active chronic HBV infection and who are considered new to nucleoside treatment should receive an oral dose of entecavir 0.5 mg once daily. Patients with a history of hepatitis B viremia, if they are receiving lamivudine or if they are known to have lamivudine-resistant mutations, should receive an oral dose of entecavir 1 mg once daily.

Entecavir is available as an oral solution containing 0.05 mg/ml of the drug. Therefore, 10 ml provides a 0.5-mg dose and 20 ml provides a 1-mg dose.

Both the tablets and the solution should be stored at room temperature. The solution should be protected from light. After the product is opened, it is stable until the bottle’s expiration date.

Patients should be advised to take entecavir on an empty stomach before meals. The optimal duration of entecavir therapy is unclear at this point.

**SPECIAL POPULATIONS**

On the basis of present pharmacokinetic studies, no specific dosage adjustments have been recommended for geriatric patients, liver transplant recipients who are receiving immunosuppressant therapy, or patients with hepatic impairment.

Given that entecavir decreases creatinine clearance in patients with renal impairment, the dose should be adjusted for patients whose creatinine clearance is less than 50 ml/minute, patients receiving dialysis, and patients with age-related decreased renal function (see Table 5).

**PHARMACOECONOMICS**

At a daily dosage of 0.5 mg daily, the average wholesale price (AWP) for entecavir is approximately $8,500 annually. The cost appears to be three times that of Epivir-HBV (lamivudine) and slightly more than that of Hepsera (adefovir dipivoxil), at approximately $7,000 per year. A cost-effectiveness analysis encompassing the various treatment options should be conducted in order to determine overall expenses.

**PREVENTION AND DETECTION**

HBV remains a primary concern today, because chronic HBV infection leads to increased morbidity and mortality. Only a small percentage of patients with chronic HBV infection are believed to be receiving treatment, an unfortunate circumstance that most certainly leads to complications.

Strategies to prevent HBV infection include avoidance of high-risk behaviors such as alterations in sexual practices, appropriate screening, immunizations, checking blood products used in transfusions, developing needle-exchange programs, and patient education. Routine screening can help to identify high-risk patients who are likely to contract HBV infection (Table 6).

Hepatitis B immune globulin (HBIG), administered after exposure, may benefit patients with passive immunity. More effective measures for protection against HBV infection include active immunization with appropriate vaccination recommendations against HBV before possible exposure. Despite advances with current antiviral therapy, some patients with chronic HBV infection may experience a sustained viral response even with appropriate therapy.

**FUTURE TRENDS**

Studies of investigational agents, such as lobucavir (Bristol-Myers Squibb), tenofovir (Viread), emtricitabine (Emtriva, Gilead), telbivudine (LdT, Idenix), and pradefovir (formerly remofovir, Valeant), are currently under way for the treatment of chronic HBV infection. Enhanced viral activity has sometimes been demonstrated with these new antiviral drugs over currently approved agents. Combination antiviral agents are also being studied. To date, however, combination antiviral therapy has not been found to be superior to traditional monotherapy.

It is hoped that entecavir will provide a better option than standard treatment regimens for patients with chronic HBV infection, given that this agent has been associated with very low rates of drug resistance.

In addition to antiviral therapy, advising patients to maintain a healthy lifestyle of proper diet, exercise, and avoidance of hepatotoxic agents can help prevent the morbidity and mortality associated with chronic forms of hepatitis B viremia.

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**REFERENCES**


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Table 6 Indications for Screening of Hepatitis B Virus (HBV) Infection

<table>
<thead>
<tr>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons born in endemic areas</td>
</tr>
<tr>
<td>Intravenous drug abusers</td>
</tr>
<tr>
<td>Homosexual males</td>
</tr>
<tr>
<td>Hemodialysis patients</td>
</tr>
<tr>
<td>HIV-infected patients</td>
</tr>
<tr>
<td>Patients with a history of sexually</td>
</tr>
<tr>
<td>transmitted diseases</td>
</tr>
<tr>
<td>Pregnant women</td>
</tr>
<tr>
<td>Family members, close contacts,</td>
</tr>
<tr>
<td>and sexual contacts of HBV-infected</td>
</tr>
<tr>
<td>individuals</td>
</tr>
</tbody>
</table>

Data from Lok AS, McMahon BJ. *Hepatology* 2004;39:857–861.1