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* Sections or subsections omitted from the full prescribing information are not listed

RECENT MAJOR CHANGES

10/2010

Dosage and Administration

Recommended Dosage (2.1)

Commercial use of BARACLUDE is not recommended for patients co-infected with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) who are not also receiving highly active antiretroviral therapy (HAART), because of the potential for the development of resistance to HIV nucleoside reverse transcriptase inhibitors. (5.2)

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.3)

BARACLUDE is not recommended for patients co-infected with HIV and HBV, (5.2)

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely for at least several months after discontinuation. Initiation of anti-hepatitis B therapy may be warranted. (5.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 0.5 mg and 1 mg (3, 16)

Oral solution: 0.05 mg/mL (3, 16)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Severe acute exacerbations of hepatitis B virus infection after discontinuation: Monitor hepatic function closely for at least several months. (5.1, 6.1)

Co-infection with HIV: BARACLUDE is not recommended unless the patient is also receiving HAART. (5.2)

Lactic acidosis and severe hepatomegaly with steatosis: If suspected, treatment should be suspended. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (≥3%, all severity grades) are headache, fatigue, dizziness, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy registry available. Enroll patients by calling 1-800-258-4263. (8.1)

Nursing mothers: Discontinue nursing or BARACLUDE taking into consideration the importance of BARACLUDE to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 10/2010

WARNINGS: SEVERE ACUTE EXACERBATIONS OF HEPATITIS B, PATIENTS CO-INFECTED WITH HIV AND HBV, AND LACTIC ACIDOSIS AND HEPATOMEGALY

See full prescribing information for complete boxed warning.

• Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely for at least several months after discontinuation. Initiation of anti-hepatitis B therapy may be warranted. (5.1)

• BARACLUDE is not recommended for patients co-infected with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) who are not also receiving highly active antiretroviral therapy (HAART), because of the potential for the development of resistance to HIV nucleoside reverse transcriptase inhibitors. (5.2)

• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.3)
WARNINGS: SEVERE ACUTE EXACERBATIONS OF HEPATITIS B, PATIENTS CO-INFECTED WITH HIV AND HBV, and LACTIC ACIDOSIS AND HEPATOMEGALY

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted [see Warnings and Precautions (5.1)].

Limited clinical experience suggests there is a potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if BARACLUDE (entecavir) is used to treat chronic hepatitis B virus (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 receiving highly active antiretroviral therapy (HAART) [see Warnings and Precautions (5.2)].

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 [see Warnings and Precautions (5.3)].

1 INDICATIONS AND USAGE

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

The following points should be considered when initiating therapy with 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 [see Clinical Studies (14.4)].
- Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease [see Adverse Reactions (6.1) and Clinical Studies (14.1)].
- 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 [see Warnings and Precautions (5.2) and Clinical Studies (14.1)].

2 DOSAGE AND ADMINISTRATION

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

2.1 Recommended Dosage

Compensated Liver Disease

The recommended dose of BARACLUDE for chronic hepatitis B virus infection in nucleoside-treatment-naïve adults and adolescents 16 years of age and older is 0.5 mg once daily.

The recommended dose of BARACLUDE in adults and adolescents (at least 16 years of age) with a history of hepatitis B viremia while receiving lamivudine or known lamivudine or telbivudine resistance mutations rtM204I/V with or without rtL180M, rtL80I/N, or rtV173L is 1 mg once daily.

Decompensated Liver Disease

The recommended dose of BARACLUDE for chronic hepatitis B virus infection in adults with decompensated liver disease is 1 mg once daily.

Oral Solution

BARACLUDE (entecavir) Oral Solution contains 0.05 mg of entecavir per milliliter. Therefore, 10 mL of the oral solution provides a 0.5-mg dose and 20 mL provides a 1-mg dose of entecavir.

2.2 Renal Impairment

In subjects with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased [see Clinical Pharmacology (12.3)]. Dosage adjustment is recommended for patients with creatinine clearance less than 50 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in Table 1. The once-daily dosing regimens are preferred.

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Usual Dose (0.5 mg)</th>
<th>Lamivudine-Refractory or Decompensated Liver Disease (1 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>0.5 mg once daily</td>
<td>1 mg once daily</td>
</tr>
<tr>
<td>30 to &lt;50</td>
<td>0.25 mg once dailya</td>
<td>0.5 mg once daily</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>10 to &lt;30</td>
<td>0.15 mg once dailya</td>
<td>0.3 mg once dailya</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>0.5 mg every 72 hours</td>
<td>1 mg every 72 hours</td>
<td></td>
</tr>
</tbody>
</table>

For patients on hemodialysis (CAPD), administer BARACLUDE 1 hour after the hemodialysis session.

If administered on a hemodialysis day, administer BARACLUDE after the hemodialysis session.

2.3 Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

2.4 Duration of Therapy

The optimal duration of treatment with BARACLUDE for patients with chronic hepatitis B virus infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown.

3 DOSAGE FORMS AND STRENGTHS

- BARACLUDE 0.5-mg film-coated tablets are white to off-white, triangular-shaped, and debossed with “BMS” on one side and “161” on the other side.
- BARACLUDE 1-mg film-coated tablets are pink, triangular-shaped, and debossed with “BMS” on one side and “1612” on the other side.
- BARACLUDE oral solution, 0.05-mg/mL, is a ready-to-use, orange-flavored, colorless to pale yellow, aqueous solution.

4 CONTRAINdications

None.

5 WARNINGS AND Precautions

5.1 Severe Acute Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir [see Adverse Reactions (6.1)]. 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.

5.2 Patients Co-infected with HIV and HBV

BARACLUDE has not been evaluated in HIV/HBV co-infected patients who were not simultaneously receiving effective HIV treatment. Limited clinical experience suggests there is a potential for the development of resistance to HIV 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 [see Clinical Pharmacology (12.4)]. Therefore, therapy with BARACLUDE is not recommended for HIV/HBV co-infected patients who are not also receiving 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.

5.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis

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.

A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with BARACLUDE should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Exacerbations of hepatitis after discontinuation of treatment [see Boxed Warning, Warnings and Precautions (5.1)]
- Lactic acidosis and severe hepatomegaly with steatosis [see Boxed Warning, Warnings and Precautions (5.3)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Compensated Liver Disease

Assessment of adverse reactions is based on four studies (A4630314, A463022, A463026, and A463027) in which 1720 subjects with chronic hepatitis B virus infection and compensated liver disease received double-blind treatment with BARACLUDE 0.5 mg/day (n=579), BARACLUDE 1 mg/day (n=183), or lamivudine (n=585) for up to 2 years. Median duration of therapy was 69 weeks for BARACLUDE-treated subjects and 63 weeks for lamivudine-treated subjects in Studies A463022 and A463027 and 73 weeks for BARACLUDE-treated subjects and 51 weeks for lamivudine-treated subjects in Studies A463026 and A463014. The safety profiles of BARACLUDE and lamivudine were comparable in these studies.
The most common adverse reactions of any severity (≥3%) with at least a possible relation to study drug for BARACLUDE-treated subjects were headache, fatigue, dizziness, and nausea. The most common adverse reactions among lamivudine-treated subjects were headache, fatigue, and dizziness. One percent of BARACLUDE-treated subjects in these four studies compared with 4% of lamivudine-treated subjects discontinued for adverse events or abnormal laboratory test results.

Clinical adverse reactions of moderate-severity intensity and considered at least possibly related to treatment occurring during therapy in four clinical studies in which BARACLUDE was compared with lamivudine are presented in Table 2.

### Table 2: Clinical Adverse Reactions of Moderate–Severe Intensity (Grades 2–4) Reported in Four Entecavir Clinical Trials Through 2 Years

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>BARACLUDE 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>BARACLUDE 1 mg</th>
<th>Lamivudine 100 mg</th>
<th>Lamivudine-refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade 2–4 adverse reaction</td>
<td>15%</td>
<td>18%</td>
<td>22%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>&lt;1%</td>
<td>0</td>
<td>1%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0</td>
<td>&lt;1%</td>
<td></td>
</tr>
</tbody>
</table>

*Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

**Includes Study A463022 and A463027.**

### Laboratory Abnormalities

Frequencies of selected treatment-emergent laboratory abnormalities reported during therapy in four clinical trials of BARACLUDE compared with lamivudine are listed in Table 3.

### Table 3: Selected Treatment-Emergent Laboratory Abnormalities Reported in Four Entecavir Clinical Trials Through 2 Years

<table>
<thead>
<tr>
<th>Nucleoside-Naïvea</th>
<th>BARACLUDE 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>BARACLUDE 1 mg</th>
<th>Lamivudine 100 mg</th>
<th>Lamivudine-refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=679</td>
<td>n=668</td>
<td>n=183</td>
<td>n=190</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT elevation</td>
<td>35%</td>
<td>36%</td>
<td>37%</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Any Grade 3–4</td>
<td>11%</td>
<td>16%</td>
<td>12%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>ALD &gt; 2 X baseline</td>
<td>2%</td>
<td>4%</td>
<td>2%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Albumin &lt; 2.5 g/dL</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin &gt; 2.5 X ULN</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Lipase ≥ 2 X ULN</td>
<td>7%</td>
<td>6%</td>
<td>7%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Creatinine ≥ 3.0 X ULN</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Confirmed creatinine increase &gt; 0.5 mg/dL</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia, fasting &gt; 250 mg/dL</td>
<td>2%</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Glycerol</td>
<td>4%</td>
<td>3%</td>
<td>4%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>9%</td>
<td>10%</td>
<td>9%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt; 50,000/mm³</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td></td>
</tr>
</tbody>
</table>

*Includes studies A463022 and A463027.**

### 6.2 Postmarketing Experience

The following adverse reactions have been reported during postmarketing use of BARACLUDE. Because these reactions were reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to BARACLUDE exposure.

**Immune system disorders:** Anaphylactoid reaction.

**Metabolism and nutrition disorders:** Lactic acidosis has been reported, often in association with hepatic decompensation, other serious medical conditions, or drug exposures. Patients with decompensated liver disease may be at higher risk for lactic acidosis.

**Hepatobiliary disorders:** Increased transaminases, skin and subcutaneous tissue disorders: Alopecia, rash.

### 7. DRUG INTERACTIONS

Since entecavir is primarily eliminated by the kidneys [see Clinical Pharmacology (12.3)], coadministration of BARACLUDE with drugs that reduce renal function or are associated with active tubular secretion may increase serum concentrations of either entecavir or the coadministered drug. Coadministration of entecavir with lamivudine, adefovir dipivoxil, or tenofovir disoproxil fumarate did not result in significant drug interactions. The effects of coadministration of BARACLUDE with other drugs that are renally eliminated or are known to affect renal function have not been evaluated, and patients should be monitored closely for adverse events when BARACLUDE is coadministered with such drugs.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of BARACLUDE in pregnant women. When pregnant rats and rabbits received entecavir at 28 and 212 times the human exposure at the highest human dose, there were no signs of embryofetal toxicity. Because animal reproduction studies are not always predictive of human response, BARACLUDE should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits.

Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to entecavir, a pregnancy registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Developmental toxicity studies were performed in rats and rabbits. There were no signs of embryofetal or maternal toxicity when pregnant animals received oral entecavir at approximately 28 (rat) and 212 (rabbit) times the human exposure achieved at the highest recommended human dose of 1 mg/day. In rats, maternal toxicity, embryofetal toxicity (resorptions), lower fetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternebrae, and phalanges), and extra lumbar vertebrae and ribs were observed at exposures 3100 times those in humans. In rabbits, embryofetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed at exposures 883 times those in humans. In a peri-postnatal study, no adverse effects on offspring occurred when rats received oral entecavir at exposures greater than 94 times those in humans.

8.2 Labor and Delivery

There are no studies in pregnant women and no data 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.

8.3 Nursing Mothers

It is not known whether BARACLUDE is excreted into human milk; however, entecavir is excreted into the milk of rats. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from BARACLUDE, a decision should be made to discontinue nursing or to discontinue BARACLUDE taking into consideration the importance of continued hepatitis B therapy to the mother and the known benefits of breastfeeding.

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of BARACLUDE did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently to treatment with the drug. There are no significant racial differences in entecavir pharmacokinetics.

8.6 Use in Racial/Ethnic Groups

Clinical studies of BARACLUDE did not include sufficient numbers of subjects from some racial/ethnic minorities (Black/African American, Hispanic) to determine whether they respond differently to treatment with the drug. There are no significant racial differences in entecavir pharmacokinetics.

8.7 Renal Impairment

Dosage adjustment of BARACLUDE is recommended for patients with creatinine clearance less than 50 mL/min, including patients on hemodialysis or CAPD [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

Liver transplant recipients: The safety and efficacy of BARACLUDE in liver transplant recipients are unknown. If BARACLUDE treatment is determined to be necessary for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus, renal function must be carefully monitored both before and during treatment with BARACLUDE [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

10 OVERDOSAGE

There is limited experience of entecavir overdose reported in patients. Healthy subjects who received single entecavir doses up to 40 mg or multiple doses up to 20 mg/day for up to 14 days had no increase in or unexpected adverse events. If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Following a single 1-mg dose of entecavir, a 4-hour hemodialysis session removed approximately 13% of the entecavir dose.

11 DESCRIPTION

BARACLUDE® is the trade name for entecavir, a guanine nucleoside analogue with selective activity against HBV. The chemical name for entecavir is 2-amino-1,3-dihydro-9-H-[1S,3R,4S]-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one, monohydrate. Its molecular formula is C₁₂H₁₅N₅O₃•H₂O, which corresponds to a molecular weight of 295.3. Entecavir has the following structural formula:

Entecavir is a white to off-white powder. It is slightly soluble in water (2.4 mg/mL), and the pH of the saturated solution in water is 7.9 at 25°C ± 0.5°C. BARACLUDE film-coated tablets are available for oral administration in strengths of 0.5 mg and 1 mg of entecavir. BARACLUDE 0.5-mg and 1-mg film-coated tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, and magnesium stearate. The tablet coating contains titanium dioxide, hypromellose, polyethylene glycol 400, polysorbate 80 (0.5-mg tablet only), and iron oxide red (1-mg tablet only). BARACLUDE Oral Solution is available for oral administration as a ready-to-use solution containing 0.05 mg of entecavir per milliliter. BARACLUDE Oral Solution contains the following inactive ingredients: maltitol, sodium citrate, citric acid, methylparaben, propylparaben, and orange flavor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Entecavir is an antiviral drug [see Clinical Pharmacology (12.4)].

12.3 Pharmacokinetics

The single- and multiple-dose pharmacokinetics of entecavir were evaluated in healthy subjects and subjects with chronic hepatitis B virus infection.

Absorption

Following oral administration in healthy subjects, entecavir peak plasma concentrations occurred between 0.5 and 1.5 hours. Following multiple daily doses ranging from 0.1 to 1.0 mg, Cmax and area under the concentration-time curve (AUC) at steady state increased in proportion to dose. Steady state was achieved after 6 to 10 days of once-daily administration with approximately 2-fold accumulation. For a 0.5-mg oral dose, Cmax at steady state was 4.2 ng/mL and trough plasma concentration (Ctrough) was 0.3 ng/mL. For a 1-mg oral dose, Cmax was 8.2 ng/mL and Ctrough was 0.5 ng/mL. In healthy subjects, the bioavailability of the tablet was 100% relative to the oral solution. The oral solution and tablet may be used interchangeably.

Effects of food on oral absorption: Oral administration of 0.5 mg of entecavir with a standard high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) resulted in a delay in absorption (1.0–1.5 hours fed vs. 0.75 hours fasted), a decrease in Cmax of 44%–46%, and a decrease in AUC of 18%–20% [see Dosage and Administration (2.2)].

Distribution

Based on the pharmacokinetic profile of entecavir after oral dosing, the estimated apparent volume of distribution is in excess of total body water, suggesting that entecavir is extensively distributed into tissues.

Binding of entecavir to human serum proteins in vitro was approximately 13%.

Metabolism and Elimination

Following administration of 14C-entecavir in humans and rats, no oxidative or acetylated metabolites were observed. Minor amounts of phase II metabolites (glucuronide and sulfate conjugates) were observed. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system [see Drug Interactions; below].

After reaching peak concentration, entecavir plasma concentrations decreased in a bi-exponential manner with a terminal elimination half-life of approximately 128–149 hours. The observed drug accumulation index is approximately 2-fold with once-daily dosing, suggesting an effective accumulation half-life of approximately 24 hours. Entecavir is predominantly eliminated by the kidney with urinary recovery of unchanged drug at steady state ranging from 62% to 73% of the administered dose. Renal clearance is independent of dose and ranges from 360 to 471 mL/min suggesting that entecavir undergoes both glomerular filtration and net tubular secretion [see Drug Interactions (7)].

Special Populations

Gender: There are no significant gender differences in entecavir pharmacokinetics.

Race: There are no significant racial differences in entecavir pharmacokinetics.

Elderly: The effect of age on the pharmacokinetics of entecavir was evaluated following administration of a single 1-mg oral dose in healthy young and elderly volunteers. Entecavir AUC was 29.3% greater in elderly subjects compared to young subjects. The disparity in exposure between elderly and young subjects was most likely attributable to differences in renal function. Dosage adjustment of BARACLUDE should be based on the renal function of the patient, rather than age [see Dosage and Administration (2.2)].
**BARACLUDE® (entecavir)**

Pediatrics: Pharmacokinetic studies have not been conducted in children.

**Renal Impairment:** The pharmacokinetics of entecavir following a single 1-mg dose were studied in subjects (without chronic hepatitis B virus infection) with selected degrees of renal impairment, including subjects whose renal impairment was managed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Results are shown in Table 5 (see Dosage and Administration [2.2]).

Table 5: Pharmacokinetic Parameters in Subjects with Selected Degrees of Renal Function

<table>
<thead>
<tr>
<th>Renal Function Group</th>
<th>Baseline Creatinine Clearance (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unimpaired</td>
</tr>
<tr>
<td>CL(_{\text{max}}) (ng/mL)</td>
<td>(107.9) (37.2)</td>
</tr>
<tr>
<td>AUC(_{0-\infty}) (ng•h/mL)</td>
<td>(27.9) (51.5)</td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
<td>(25.6) (22.8)</td>
</tr>
<tr>
<td>CLR (mL/min)</td>
<td>(363.2)</td>
</tr>
<tr>
<td>AUC(_{0-\infty}) (ng•h/mL)</td>
<td>(408.1)</td>
</tr>
<tr>
<td>CL(_{\text{t}}) (mL/min)</td>
<td>(153.7)</td>
</tr>
</tbody>
</table>

a Dosed immediately following hemodialysis.

**CLR** = renal clearance; **CL\(_{\text{t}}\)** = apparent oral clearance.

In HIV antiviral assays, entecavir was not antagonistic to the cell culture anti-HIV activity of these six NRTIs or emtricitabine at concentrations greater than 100 times the **C\(_{\text{max}}\)** of entecavir using the 1-mg dose.

**Antiviral Activity against HIV**

A comprehensive analysis of the inhibitory activity of entecavir against a panel of laboratory and clinical HIV type 1 (HIV-1) isolates using a variety of cells and assay conditions yielded EC\(_{50}\) values ranging from 0.026 to >100 \(\mu\)M; the lower EC\(_{50}\) values were observed when decreased levels of virus were used in the assay, in cell culture, entecavir was selected for an M184 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.

**Resistance in Cell Culture**

In cell-based assays, 8- to 30-fold reductions in entecavir phenotypic susceptibility were observed for lamivudine-resistant strains. Further reductions (>70-fold) in entecavir phenotypic susceptibility of the preclinical resistant substitutions rtM204/V with or without rtL180M along with additional substitutions at residues rtI184, rtS202, or rtM250, or a combination of these substitutions with or without an rtL180 substitution in the HBV reverse transcriptase.

**Clinical Studies**

**Nucleoside-naive subjects:** Genotypic evaluations were performed on evaluable samples (>300 copies/mL serum HBV DNA) from 562 subjects who were treated with BARACLUDE for up to 96 weeks in nucleoside-naive studies (AI463022, AI463027, and rollover study AI463901). By Week 96, evidence of emerging amino acid substitution rtS202G with rtM204V and rtL180M substitutions was detected in the HBV of 2 subjects (2/562=0.3%), and 1 of them experienced virologic rebound (%1log10 increase above nadir). In addition, emerging amino acid substitutions at rtM204I/V and rtL180M, rtL80I, or rtV173L, which conferred decreased phenotypic susceptibility to entecavir, were absent at Weeks 48, 96, rtS202G, or rtM250, or a combination in the HBV of 8 subjects (3/562=0.5%) who experienced virologic rebound.

For subjects who continued treatment beyond 48 weeks, 75% (202/269) had HBV DNA <300 copies/mL at end of dosing (up to 96 weeks).

**HBeAg-positive (n=243) and -negative (n=39) treatment-naïve subjects** who failed to achieve the study-defined complete response by 96 weeks were offered continued entecavir treatment in a subset analysis. For the HBeAg-positive group, virologic response was ≥1 log10 decrease above nadir, and for HBeAg-negative was ≥1 log10 decrease at Week 96. For patients experiencing virologic rebound (%1log10 increase above nadir) and 4 of whom were never suppressed <300 copies/mL. The HBV from 4 of these subjects had entecavir resistance substitutions at baseline and acquired further changes on entecavir treatment. In addition to the 22 subjects, 3 patients experienced virologic rebound with the emergence of rtM204V and rtL180M, rtS202G, or rtV173L/rtM substitutions at Weeks 48, 96, 144, and 240 (including end of dosing).

Lamivudine-refractory subjects (n=157) who failed to achieve the study-defined complete response by Week 96 were offered continued entecavir treatment. Subjects received 1 mg entecavir once daily for up to an additional 144 weeks. Of these 282 subjects, 141 HBeAg-positive and 8 HBeAg-negative subjects entered the long-term follow-up rollover study and were evaluated for entecavir resistance. Of the 149 subjects entering the rollover study, 88% (131/149), 92% (137/149), and 92% (137/149) attained serum HBV DNA <300 copies/mL by Weeks 144, 192, and 240 (including end of dosing), respectively. No novel entecavir resistance-associated substitutions were identified in a comparison of the genotypes of evaluable isolates with their respective baseline isolates. The cumulative probability of developing rtI184, rtS202, or rtM250 entecavir resistance-associated substitutions (in the presence of rtM204V and rtL180M substitutions) at Weeks 48, 96, 144, and 240 was 0.2%, 0.5%, 1.2%, 1.2%, and 1.2%, respectively.

**Lamivudine-refractory subjects:** Genotypic evaluations were performed on evaluable samples from 190 subjects treated with BARACLUDE for up to 96 weeks in studies of the antiretroviral HIV therapy (AI463022, AI463015, AI463027, and rollover study AI463901). By Week 96, resistance-associated amino acid substitutions at rtS202G, rtI184, or rtM250, or with or without rtL180M changes, in the presence of amino acid substitutions rtM204I/V with or without rtL180M, rtL80I, or rtV173L/rtM emerged in the HBV from 22 subjects (2/22=10%). Of these subjects with virologic rebound (%1log10 increase above nadir) and 4 of whom were never suppressed <300 copies/mL. The HBV from 4 of these subjects had entecavir resistance substitutions at baseline and acquired further changes on entecavir treatment. In addition to the 22 subjects, 3 subjects experienced virologic rebound with the emergence of rtM204V and rtL180M, rtS202G, or rtV173L/rtM. For isolates from subjects who experienced virologic rebound with the emergence of resistance substitutions (n=19), the median fold change from baseline lamivudine-resistant \\(^*\) was 106-fold higher than that observed in the nucleoside therapy group (AI463022, AI463027, and rollover study AI463901). By Week 96, resistance-associated amino acid substitutions at rtS202G, rtI184, or rtM250 were observed in 19/46 (41%) of subjects entering the rollover study with the emergence of resistance substitutions rtM204V with or without rtL180M, rtL80I, or rtV173L/rtM substitutions at Weeks 48, 96, 144, and 240 (including end of dosing).

**12.4 Microbiology**

**Mechanism of Action**

Entecavir, a guanosine nucleoside analogue with activity against HBV reverse transcriptase (rt), is efficiently phosphorylated to the active triphosphate form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine triphosphate, entecavir triphosphate functionally inhibits all three activities of the HBV reverse transcriptase: (1) base priming, (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand of HBV DNA. Entecavir triphosphate is a weak inhibitor of cellular DNA polymerases \(\alpha\), \(\beta\), and \(\lambda\) and mitochondrial DNA polymerase with \(K_I\) values ranging from 18 to >160 \(\mu\)M.

**Antiviral Activity**

Entecavir inhibited HBV DNA synthesis (50% reduction, EC\(_{50}\)) at a concentration of 0.004 \(\mu\)M in human HepG2 cells transfected with wild-type HBV. The median EC\(_{50}\) value for entecavir against lamivudine-resistant HBV (rtL180M, rtM204V) was 0.026 \(\mu\)M (range 0.010–0.059 \(\mu\)M).

The coadministration of HBV nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) with BARACLUDE is unlikely to reduce the antiviral efficacy of BARACLUDE against HBV or of any of these agents against HIV. In HBV combination assays in cell culture, abacavir, didanosine, lamivudine, stavudine, tenofovir, or zidovudine were not antagonistic to the anti-HBV activity of entecavir over a wide range of concentrations.
13.1 NONCLINICAL TOXICOLOGY

Long-term oral carcinogenicity studies of entecavir in mice and rats were carried out at exposures up to approximately 42 times (mice) and 35 times (rats) those observed in humans at the highest recommended dose of 1 mg/day. In mouse and rat studies, entecavir was positive for carcinogenic findings.

In mice, lung adenomas were increased in males and females at exposures 3 and 40 times those in humans. Lung carcinomas in both male and female mice were increased at exposures 40 times those in humans. Combined lung adenomas and carcinomas were increased in male mice at exposures 3 times and in female mice at exposures 40 times those in humans. Tumor development was preceded by pneumocyte proliferation in the lung, which was not observed in rats, dogs, or monkeys administered entecavir, supporting the conclusion that lung tumors in mice may be a species-specific event. Hepatocellular carcinomas were increased in males and combined liver adenomas and carcinomas were also increased at exposures 42 times those in humans. Vascular tumors in male mice (hemangioendothelioma of skin and hemangioendotheliomas of spleen) were increased at exposures 40 times those in humans. In rats, hepatocellular adenomas were increased in females at exposures 24 times those in humans; combined adenomas and carcinomas were also increased in females at exposures 24 times those in humans. Brain gliomas were induced in both males and females at exposures 32 and 24 times those in humans. Skin fibromas were induced in females at exposures 4 times those in humans.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Entecavir was clastogenic to human lymphocyte cultures. Entecavir was not mutagenic in the Ames bacterial reverse mutation assay using S. typhimurium and E. coli strains in the presence or absence of metabolic activation, a mammalian-cell gene mutation assay, and a transformation assay with Syrian hamster embryo cells. Entecavir was also negative in an oral micronucleus study and an oral DNA repair study in rats. In reproductive toxicity studies, in which animals were administered entecavir at up to 30 mg/kg for up to 4 weeks, no evidence of impaired fertility was seen in male or female rats at systemic exposures greater than 90 times those achieved in humans at the highest recommended dose of 1 mg/day. In rodent and dog toxicity studies, seminiferous tubular degeneration was observed at exposures 35 times or greater than those achieved in males. No testicular changes were evident in monkeys.

14 CLINICAL STUDIES

The safety and efficacy of BARACLUDE were evaluated in three Phase 3 active-controlled trials [see Clinical Studies (14.1 and 14.2)]. These studies included 1633 subjects 18 years of age or older with chronic hepatitis B virus infection (serum HBsAg-positive for at least 6 months) accompanied by evidence of viral replication (detectable serum HBV DNA, as measured by the bDNA hybridization or PCR assay). Subjects had persistently elevated ALT levels at least 1.3 times ULN and chronic inflammation on liver biopsy compatible with a diagnosis of chronic viral hepatitis. The safety and efficacy of BARACLUDE were also evaluated in a study of 191 HBV-infected subjects with decompensated liver disease and in a study of 68 subjects co-infected with HBV and HIV [see Clinical Studies (14.1)].

14.1 Outcomes at 48 Weeks

Nucleoside-naive subjects with compensated liver disease

HBsAg-positive: Study AI463022 was a multinational, randomized, double-blind study of BARACLUDE 0.5 mg once daily versus lamivudine 100 mg once daily for a minimum of 52 weeks. Subjects included 715 randomized nucleoside-naive subjects with chronic hepatitis B virus infection, compensated liver disease, and detectable HBsAg. The mean age of subjects was 35 years, 75% were male, 57% were Asian, 40% were Caucasian, and 13% had previously received interferon-α. At baseline, subjects had a mean Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA as measured by Roche COBAS AmpliCope® PCR assay was 9.66 log₁₀ copies/mL, and mean serum ALT level was 143 U/L. Paired, adequate liver biopsy samples were available for 89% of subjects.

HBsAg-negative (anti-HBe-positive/HBV DNA-positive): Study AI463027 was a multinational, randomized, double-blind study of BARACLUDE 0.5 mg once daily versus lamivudine 100 mg once daily for a minimum of 52 weeks in 638 (of 648 randomized) nucleoside-naive subjects with HBsAg-negative (HBeAb-positive) chronic hepatitis B virus infection and compensated liver disease. The mean age of subjects was 44 years, 76% were male, 39% were Asian, 58% were Caucasian, and 13% had previously received interferon-α. At baseline, subjects had a mean Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA as measured by Roche COBAS AmpliCope PCR assay was 7.58 log₁₀ copies/mL, and mean serum ALT level was 142 U/L. Paired, adequate liver biopsy samples were available for 88% of subjects.
Subjects Co-infected with HIV and HBV

Study A1463038 was a randomized, double-blind, placebo-controlled study of BARACLUDE versus placebo in 68 subjects co-infected with HIV and HBV who experienced recurrence of HBV viremia while receiving a lamivudine-containing highly active antiretroviral (HAART) regimen. Subjects continued their lamivudine-containing HAART regimen (lamivudine dose 300 mg/day) and were assigned to either BARACLUDE 1 mg once daily (51 subjects) or placebo (17 subjects) for 24 weeks followed by an open-label phase for an additional 24 weeks where all subjects received BARACLUDE. At baseline, subjects had a mean serum HBV DNA level by PCR of 9.13 log_{10} copies/mL. Ninety-nine percent of subjects were HBeAg-positive at baseline, with a mean baseline ALT level of 71.5 U/L. Median HIV RNA level remained stable at approximately 2 log_{10} copies/mL through 24 weeks of blinded therapy. Virologic and biochemical endpoints at Week 24 are shown in Table 11. There are no data in patients with HIV/HBV co-infection who have not received prior lamivudine therapy. BARACLUDE has not been evaluated in HIV/HBV co-infected patients who were not simultaneously receiving effective HIV treatment [see Warnings and Precautions (5.2)].

### Table 11: Virologic and Biochemical Endpoints at Week 24, Study A1463038

<table>
<thead>
<tr>
<th>BARACLUDE 1 mg&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Placebo&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=51</td>
<td>n=17</td>
</tr>
<tr>
<td>HBV DNA&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Proportion undetectable (&lt;300 copies/mL)</td>
<td>6%</td>
</tr>
<tr>
<td>Mean change from baseline (log_{10} copies/mL)</td>
<td>-3.65</td>
</tr>
<tr>
<td>ALT normalization (&lt;1 X ULN)</td>
<td>34%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> All subjects also received a lamivudine-containing HAART regimen.

### Subjects Co-infected with HIV and HBV

Study A1463038 was a randomized, open-label study of BARACLUDE 1 mg once daily versus adefovir dipivoxil 10 mg once daily for 24 weeks. Subjects were randomized to lamivudine-refractory or lamivudine-naive subjects. Lamivudine-refractory subjects were those who were not lamivudine-resistant by resistance testing and who had a history of lamivudine therapy. Lamivudine-naive subjects were those who had not previously received lamivudine therapy. Subjects were HBeAg-positive at baseline. The mean change from baseline HBV DNA by PCR was -4.20 log_{10} copies/mL, and 37% of subjects with baseline HBV DNA <300 copies/mL achieved ALT normalization (<1 X ULN).

### Table 8: Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Lamivudine-Refractory Subjects in Study A1463026

<table>
<thead>
<tr>
<th>BARACLUDE 1 mg</th>
<th>Lamivudine 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=124&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n=116&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HBV DNA&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Proportion undetectable (&lt;300 copies/mL)</td>
<td>19%</td>
</tr>
<tr>
<td>Mean change from baseline (log_{10} copies/mL)</td>
<td>-5.11</td>
</tr>
<tr>
<td>ALT normalization (&lt;1 X ULN)</td>
<td>61%</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>8%</td>
</tr>
</tbody>
</table>

<sup>a</sup> ROCHE COBAS Amplicor PCR assay (LLDQ = 300 copies/mL).

### Table 9: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Lamivudine-Refractory Subjects in Study A1463026

<table>
<thead>
<tr>
<th>BARACLUDE 1 mg</th>
<th>Lamivudine 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=141</td>
<td>n=145</td>
</tr>
<tr>
<td>HBV DNA&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Proportion undetectable (&lt;300 copies/mL)</td>
<td>57%</td>
</tr>
<tr>
<td>Mean change from baseline (log_{10} copies/mL)</td>
<td>61%</td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>5%</td>
</tr>
<tr>
<td>Normalization of ALT (&lt;1 X ULN)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>49/78 (63%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> ROCHE COBAS Amplicor PCR assay (LLDQ = 300 copies/mL).

### Table 10: Selected Endpoints at Week 48, Subjects with Decompensated Liver Disease, Study A1463048

<table>
<thead>
<tr>
<th>BARACLUDE 1 mg</th>
<th>Adefovir Dipivoxil</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=100&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n=91&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HBV DNA&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Proportion undetectable (&lt;300 copies/mL)</td>
<td>57%</td>
</tr>
<tr>
<td>Stable or improved CTP score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>61%</td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>5%</td>
</tr>
<tr>
<td>Normalization of ALT (&lt;1 X ULN)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>49/78 (63%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> For subjects originally assigned to BARACLUDE, at the end of the open-label phase (Week 48), 8% of subjects had HBV DNA <300 copies/mL by PCR, the mean change from baseline HBV DNA by PCR was -4.20 log_{10} copies/mL. 57% of subjects with abnormal ALT at baseline achieved ALT normalization (<1 X ULN).

### 14.2 Outcomes beyond 48 Weeks

The optimal duration of therapy with BARACLUDE is unknown. According to protocol-mandated criteria in the Phase 3 clinical trials, subjects discontinued BARACLUDE or lamivudine treatment after 52 weeks according to a definition of response based on HBV virologic suppression (<0.7 MEq/mL by bDNA assay) and loss of HBeAg (in HBeAg-positive subjects) or ALT <1.25 X ULN (in HBeAg-negative subjects) at Week 48. Subjects who achieved virologic suppression but did not have serologic response (HBeAg-positive) or did not achieve ALT <1.25 X ULN (HBeAg-negative) continued blinded dosing through 96 weeks or until the response criteria were met. These protocol-specified subject management guidelines are not intended as guidance for clinical practice.

### Nucleoside-naïve subjects: Among nucleoside-naïve, HBeAg-positive subjects (Study A1463022), 243 (69%) BARACLUDE-treated subjects and 164 (46%) lamivudine-treated subjects continued blinded treatment for up to 96 weeks. Of those continuing blinded treatment in Year 2, 180 (74%) BARACLUDE subjects and 60 (37%) lamivudine subjects achieved HBV DNA <300 copies/mL by PCR at the end of dosing (up to 96 weeks). 193 (79%) BARACLUDE subjects achieved ALT <1 X ULN compared to 112 (68%) lamivudine subjects, and HBeAg seroconversion occurred in 26 (11%) BARACLUDE subjects and 20 (12%) lamivudine subjects.

### Nucleoside-refractory subjects: Among nucleoside-refractory, HBeAg-positive subjects (Study A1463027), 26 (8%) BARACLUDE-treated subjects and 28 (9%) lamivudine-treated subjects continued blinded treatment for up to 96 weeks. In this small cohort continuing treatment in Year 2, 22 BARACLUDE and 16 lamivudine subjects had HBV DNA <300 copies/mL by PCR, and 7 and 6 subjects, respectively, had ALT <1 X ULN at the end of dosing (up to 96 weeks).

### Lamivudine-refractory subjects: Among lamivudine-refractory subjects (Study A1463026), 77 (55%) BARACLUDE-treated subjects and 3 (2%) lamivudine-treated subjects continued blinded treatment for up to 96 weeks. In this cohort of BARACLUDE subjects, 31 (40%) subjects achieved HBV DNA <300 copies/mL. 62 (81%) BARACLUDE subjects had ALT <1 X ULN, and 8 (10%) subjects demonstrated HBeAg seroconversion at the end of dosing.
**BARACLUDE® (entecavir)** Tablets and Oral Solution are available in the following strengths and configurations of plastic bottles with child-resistant closures:

<table>
<thead>
<tr>
<th>Product Description</th>
<th>Quantity</th>
<th>NDC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>White to off-white, triangular-shaped tablet, debossed with “BMS” on one side and “1611” on the other side.</td>
<td>30 tablets</td>
<td>0003-1611-12</td>
</tr>
<tr>
<td>Pink, triangular-shaped tablet, debossed with “BMS” on one side and “1612” on the other side.</td>
<td>90 tablets</td>
<td>0003-1611-13</td>
</tr>
<tr>
<td>Ready-to-use, orange-flavored, clear, colorless to pale yellow, aqueous solution in a 260-mL bottle.</td>
<td>210 mL</td>
<td>0003-1614-12</td>
</tr>
</tbody>
</table>

BARACLUDE Oral Solution is a ready-to-use product; dilution or mixing with water or any other solvent or liquid product is not recommended. Each bottle of the oral solution is accompanied by a dosing spoon that is calibrated in 1-mL increments up to 10 mL [see Patient Counseling Information (17.1)].

Storage

BARACLUDE Tablets should be stored in a tightly closed container at 25°C (77°F); excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].

BARACLUDE Oral Solution should be stored in the outer carton at 25°C (77°F); excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light. After opening, the oral solution can be used up to the expiration date on the bottle. The bottle and its contents should be discarded after the expiration date.

**17.1 Information about Treatment**

Physicians should inform their patients of the following important points when initiating BARACLUDE treatment:

- Patients should remain under the care of a physician while taking BARACLUDE. They should discuss any new symptoms or concurrent medications with their physician.
- 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.
- Patients should be advised to take BARACLUDE on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).
- Patients using the oral solution should be instructed to hold the dosing spoon in a vertical position and fill it gradually to the mark corresponding to the prescribed dose. Rinsing of the dosing spoon with water is recommended after each daily dose.
- Patients should be advised to take a missed dose as soon as remembered unless it is almost time for the next dose. Patients should not take two doses at the same time.
- Patients should be advised that treatment with BARACLUDE will not cure HBV.
- Patients should be informed that BARACLUDE may lower the amount of HBV in the body, may lower the ability of HBV to multiply and infect new liver cells, and may improve the condition of the liver.
- Patients should be informed that it is not known whether BARACLUDE will reduce their chances of getting liver cancer or cirrhosis.

**17.2 Post-treatment Exacerbation of Hepatitis**

Patients should be informed that deterioration of liver disease may occur in some cases if treatment is discontinued, and that they should discuss any change in regimen with their physician.

**17.3 HIV/HBV Co-infection**

Patients should be offered HIV antibody testing before starting BARACLUDE therapy. They should be informed that if they have HIV infection and are not receiving effective HIV treatment, BARACLUDE may increase the chance of HIV resistance to HIV medication.

**FDA-approved Patient Labeling**

**BARACLUDE® (BEAR ah klude)**

(entecavir)

**Patient Information**

**BARACLUDE** Tablets and Oral Solution

Read this Patient Information before you start taking BARACLUDE and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about BARACLUDE?

1. Your hepatitis B virus infection may get worse if you stop taking BARACLUDE. This usually happens within 6 months after stopping BARACLUDE.
   - Take BARACLUDE exactly as prescribed.
   - Do not run out of BARACLUDE.
   - Do not stop BARACLUDE without talking to your healthcare provider.
   - Your healthcare provider should monitor your health and do regular blood tests to check your liver if you stop taking BARACLUDE.

2. If you have or get HIV that is not being treated with medicines while taking BARACLUDE, the HIV virus may develop resistance to certain HIV medicines and become harder to treat. You should get an HIV test before you start taking BARACLUDE and anytime after that when there is a chance you were exposed to HIV.

**BARACLUDE can cause serious side effects including:**

3. Lactic acidosis (buildup of acid in the blood). Some people who have taken BARACLUDE or medicines like BARACLUDE (a nucleoside analogue) have developed a serious condition called lactic acidosis. Lactic acidosis is a serious medical emergency that can cause death. Lactic acidosis must be treated in the hospital. Reports of lactic acidosis with BARACLUDE generally involved patients who were seriously ill due to their liver disease or other medical condition.

Call your healthcare provider right away if you get any of the following signs or symptoms of lactic acidosis:

- You feel very weak or tired.
- You have unusual (not normal) muscle pain.
- You have trouble breathing.
- You have stomach pain with nausea and vomiting.
- You feel cold, especially in your arms and legs.
- You feel dizzy or light-headed.
- You have a fast or irregular heartbeat.

4. Serious liver problems. Some people who have taken medicines like BARACLUDE have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Hepatomegaly with steatosis is a serious medical emergency that can cause death.

Call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:

- Your skin or the white part of your eyes turns yellow (jaundice).
- Your urine turns dark.
- Your bowel movements (stools) turn light in color.
- You don’t feel like eating food for several days or longer.
- You feel sick to your stomach (nausea).
- You have lower stomach pain.

You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight, or have been taking nucleoside analogue medicines, like BARACLUDE, for a long time.

What is BARACLUDE?

BARACLUDE is a prescription medicine used to treat chronic hepatitis B virus (HBV) in adults who have active liver damage.

- BARACLUDE will not cure HBV.
- BARACLUDE may lower the amount of HBV in the body.
- BARACLUDE may lower the ability of HBV to multiply and infect new liver cells.
- BARACLUDE may improve the condition of your liver.
- It is not known whether BARACLUDE will reduce your chances of getting liver cancer or liver damage (cirrhosis), which may be caused by chronic HBV infection.
- It is not known if BARACLUDE is safe and effective for use in children.
BARACLUDE® (entecavir)

What should I tell my healthcare provider before taking BARACLUDE?

Before you take BARACLUDE, tell your healthcare provider if you:

- have kidney problems. Your BARACLUDE dose or schedule may need to be changed.
- have received medicine for HBV before. Some people, especially those who have already been treated with certain other medicines for HBV infection, may develop resistance to BARACLUDE. These people may have less benefit from treatment with BARACLUDE and may have worsening of hepatitis after resistant virus appears. Your healthcare provider will test the level of the hepatitis B virus in your blood regularly.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if BARACLUDE will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- Pregnancy Registry. If you take BARACLUDE while you are pregnant, talk to your healthcare provider about how you can take part in the BARACLUDE Pregnancy Registry. The purpose of the pregnancy registry is to collect information about the health of you and your baby.
- are breast-feeding or plan to breast-feed. It is not known if BARACLUDE can pass into your breast milk. You and your healthcare provider should decide if you will take BARACLUDE or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take BARACLUDE?

- Take BARACLUDE exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much BARACLUDE to take.
- Your healthcare provider will tell you when and how often to take BARACLUDE.
- Take BARACLUDE on an empty stomach, at least 2 hours after a meal and at least 2 hours before the next meal.
- If you are taking BARACLUDE Oral Solution, carefully measure your dose with the spoon provided, as follows:
  - Hold the spoon in a vertical (upright) position and fill it gradually to the mark corresponding to the prescribed dose. Holding the spoon with the volume marks facing you, check that it has been filled to the proper mark.
  - Swallow the medicine directly from the measuring spoon.
  - After each use, rinse the spoon with water and allow it to air dry.
  - If you lose the spoon, call your pharmacist or healthcare provider for instructions.
- Do not change your dose or stop taking BARACLUDE without talking to your healthcare provider.
- If you forget to take BARACLUDE, take it as soon as you remember and then take your next dose at its regular time. If it is almost time for your next dose, skip the missed dose. Do not take two doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do.
- When your supply of BARACLUDE starts to run low, call your healthcare provider or pharmacy for a refill. Do not run out of BARACLUDE (entecavir).
- If you take too much BARACLUDE, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of BARACLUDE?

BARACLUDE may cause serious side effects. See “What is the most important information I should know about BARACLUDE?”

The most common side effects of BARACLUDE include:

- headache
- tiredness
- dizziness
- nausea.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of BARACLUDE. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

BARACLUDE® (entecavir)

How should I store BARACLUDE?

- Store BARACLUDE Tablets or Oral Solution at room temperature, between 59° F to 86° F (15° C to 30° C).
- Keep BARACLUDE Tablets in a tightly closed container.
- Do not store BARACLUDE Tablets in a damp place such as a bathroom medicine cabinet or near the kitchen sink.
- Store BARACLUDE Oral Solution in the original carton, and keep BARACLUDE Oral Solution out of the light.
- Safely throw away BARACLUDE that is out of date or no longer needed. Dispose of unused medicines through community take-back disposal programs when available or place BARACLUDE in an unrecognizable closed container in the household trash.

Keep BARACLUDE and all medicines out of the reach of children.

General information about the safe and effective use of BARACLUDE

BARACLUDE does not stop you from spreading the hepatitis B virus (HBV) to others by sex, sharing needles, or being exposed to your blood. Talk with your healthcare provider about safe sexual practices that protect your partner. Never share needles. Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades. A shot (vaccine) is available to protect people at risk from becoming infected with HBV.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use BARACLUDE for a condition for which it was not prescribed. Do not give BARACLUDE to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information Leaflet summarizes the most important information about BARACLUDE. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BARACLUDE that is written for healthcare professionals.

For more information, go to www.Barclude.com or call 1-800-321-1335.

What are the ingredients in BARACLUDE?

Active ingredient: entecavir

Inactive ingredients in BARACLUDE Tablets: lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, magnesium stearate. Tablet film-coat: titanium dioxide, hypromellose, polyethylene glycol 400, polysorbate 80 (0.5-mg tablet only), and iron oxide red (1-mg tablet only).

Inactive ingredients in BARACLUDE Oral Solution: maltitol, sodium citrate, citric acid, methylparaben, propylparaben, and orange flavor.

Bristol-Myers Squibb

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This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.

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