BARACLUDE® (entecavir) tablets, for oral use
BARACLUDE® (entecavir) oral solution
Initial U.S. Approval: 2005

WARNING: 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 analogue inhibitors. (5.3)

INDICATIONS AND USAGE
BARACLUDE is a hepatitis B virus nucleoside analogue reverse transcriptase inhibitor indicated for the treatment of chronic hepatitis B virus infection in adults and children at least 2 years of age with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. (1)

DOSAGE AND ADMINISTRATION
- Nucleoside-inhibitor-treatment-naïve with compensated liver disease (greater than or equal to 16 years old): 0.5 mg once daily. (2.2)
- Nucleoside-inhibitor-treatment-naïve and lamivudine-experienced pediatric patients at least 2 years of age and weighing at least 10 kg: dosing is based on weight. (2.3)

FULL PRESCRIBING INFORMATION: CONTENTS *
WARNING: SEVERE ACUTE EXACERBATIONS OF HEPATITIS B, PATIENTS CO-INFECTED WITH HIV AND HBV, AND LACTIC ACIDOSIS AND HEPATOMEGALY

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Timing of Administration
2.2 Recommended Dosage in Adults
2.3 Recommended Dosage in Pediatric Patients
2.4 Renal Impairment
2.5 Hepatic Impairment
2.6 Duration of Therapy
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Severe Acute Exacerbations of Hepatitis B
5.2 Patients Co-infected with HIV and HBV
5.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Pediatric Use
8.4 Geriatric Use
8.5 Racial/Ethnic Groups
8.6 Renal Impairment
8.7 Liver Transplant Recipients

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.4 Microbiology

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
14.1 Outcomes in Adults
14.2 Outcomes in Pediatric Subjects

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
2.1 Timing of Administration

Viral replication and either evidence of persistent elevations in serum aminotransferases in patients with 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 also receiving highly active antiretroviral therapy (HAART) [see Warnings and Precautions (5.2)].

Limited clinical experience suggests there is a potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if BARACLUDE is used to treat chronic hepatitis B virus (HBV) infection in patients with HIV infection that is not being treated. Therapy with BARACLUDE is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART) [see Warnings and Precautions (5.2)].

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogue inhibitors alone or in combination with antiretrovirals [see Warnings and Precautions (5.3)].

2.2 Recommended Dosage in Adults

Compensated Liver Disease

The recommended dose of BARACLUDE for chronic hepatitis B virus infection in nucleoside-inhibitor-treatment-naive 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 substitutions rtM204I/V with or without rtL180M, rtL80I/V, 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.

2.3 Recommended Dosage in Pediatric Patients

Table 1 describes the recommended dose of BARACLUDE for pediatric patients 2 years of age or older and weighing at least 10 kg. The oral solution should be used for patients with body weight up to 30 kg.

Table 2: Recommended Dosage of BARACLUDE in Adult Patients with Renal Impairment

<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 or greater</td>
<td>0.5 mg once daily</td>
<td>1 mg once daily</td>
</tr>
<tr>
<td>30 to less than 50</td>
<td>0.25 mg once daily¹</td>
<td>0.5 mg once daily</td>
</tr>
<tr>
<td>OR</td>
<td>0.5 mg every 48 hours</td>
<td>1 mg every 48 hours</td>
</tr>
<tr>
<td>10 to less than 30</td>
<td>0.15 mg once daily²</td>
<td>0.3 mg once daily</td>
</tr>
<tr>
<td>OR</td>
<td>0.5 mg every 72 hours</td>
<td>1 mg every 72 hours</td>
</tr>
<tr>
<td>Less than 10</td>
<td>0.05 mg once daily³</td>
<td>0.1 mg once daily</td>
</tr>
<tr>
<td>Hemodialysis² or CAPD</td>
<td>0.5 mg every 7 days</td>
<td>1 mg every 7 days</td>
</tr>
</tbody>
</table>

¹ For doses less than 0.5 mg, BARACLUDE Oral Solution is recommended.
² If administered on a hemodialysis day, administer BARACLUDE after the hemodialysis session.

Although there are insufficient data to recommend a specific dose adjustment of BARACLUDE in pediatric patients with renal impairment, a reduction in the dose or an increase in the dosing interval similar to adjustments for adults should be considered.

2.5 Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

2.6 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 “1611” 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, clear, colorless to pale yellow, aqueous solution. Ten milliliters of the oral solution provides a 0.5 mg dose and 20 mL provides a 1 mg dose of entecavir.

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 Microbiology (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 analogue inhibitors alone or in combination with antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside inhibitor exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogue inhibitors to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors.

Lactic acidosis with BARACLUDE use 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.
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)].

Clinical Trial Experience in Adults

Compensated Liver Disease

Assessment of adverse reactions is based on four studies (AI463014, AI463022, AI463026, and AI463027) 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=679), BARACLUDE 1 mg/day (n=183), or lamivudine (n=558) 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 AI463022 and AI463027 and 73 weeks for BARACLUDE-treated subjects and 51 weeks for lamivudine-treated subjects in Studies AI463026 and AI463014. 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 relationship 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 3.

Table 3: 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>Nucleoside-Inhibitor-Naïve</th>
<th>Lamivudine</th>
<th>BARACLUDE</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 mg n=679</td>
<td>100 mg n=668</td>
<td>1 mg n=183</td>
<td>100 mg n=190</td>
</tr>
<tr>
<td>Any Grade 2–4 adverse reaction</td>
<td>15%</td>
<td>18%</td>
<td>22%</td>
<td>23%</td>
</tr>
<tr>
<td>Gastrointestinal</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>
</tr>
<tr>
<td>Dyspepsia</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric</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>
</tr>
</tbody>
</table>

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

b Studies AI463022 and AI463027.

c Includes Study AI463026 and the BARACLUDE 1 mg and lamivudine treatment arms of Study AI463014, a Phase 2 multinational, randomized, double-blind study of three doses of BARACLUDE (0.1, 0.5, and 1 mg) once daily versus continued lamivudine 100 mg once daily for up to 52 weeks in subjects who experienced recurrent viremia on lamivudine therapy.

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 4.

Table 4: Selected Treatment-Emergent Laboratory Abnormalities Reported in Four Entecavir Clinical Trials Through 2 Years

<table>
<thead>
<tr>
<th>Test</th>
<th>Nucleoside-Inhibitor-Naïve</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg</td>
<td>n=679</td>
<td>100 mg n=668</td>
</tr>
<tr>
<td>Any Grade 3–4 laboratory abnormality</td>
<td>35%</td>
<td>36%</td>
</tr>
<tr>
<td>ALT &gt;10 x ULN and &gt;2 x baseline</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>ALT &gt;5 x ULN</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Albumin &lt;2.5 g/dL</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Total bilirubin &gt;2.5 x ULN</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Lipase &gt;2.1 x ULN</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Creatinine &gt;3 x ULN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Confirmed creatinine increase &gt;0.5 mg/dL</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Hyponatremia, fasting &gt;250 mg/dL</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Platelets &lt;50,000/mm³</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

a On-treatment value worsened from baseline to Grade 3 or Grade 4 for all parameters except albumin (any on-treatment value <2.5 g/dL), confirmed creatinine increase >0.5 mg/dL, and ALT >10 x ULN and >2 x baseline.

b Studies AI463022 and AI463027.

c Includes Study AI463026 and the BARACLUDE 1 mg and lamivudine treatment arms of Study AI463014, a Phase 2 multinational, randomized, double-blind study of three doses of BARACLUDE (0.1, 0.5, and 1 mg) once daily versus continued lamivudine 100 mg once daily for up to 52 weeks in subjects who experienced recurrent viremia on lamivudine therapy.

d Includes hematology, routine chemistries, renal and liver function tests, pancreatic enzymes, and urinalysis.

e Grade 3 = 3+, large, >500 mg/dL; Grade 4 = 4+, marked, severe.

f Grade 3 = 3+, large; Grade 4 = >4+, marked, severe, many.

ULN—upper limit of normal.

Among BARACLUDE-treated subjects in these studies, on-treatment ALT elevations greater than 10 times the upper limit of normal (ULN) and greater than 2 times baseline generally resolved with continued treatment. A majority of these exacerbations were associated with a ≥2 log₁₀/mL reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations of Hepatitis After Discontinuation of Treatment

An exacerbation of hepatitis or ALT flare was defined as ALT greater than 10 times the upper limit of normal (ULN) and greater than 2 times baseline. A subset of subjects was allowed to discontinue treatment at or after 52 weeks if they achieved a protocol-defined response to therapy. If BARACLUDE is discontinued without regard to treatment response, the rate of post-treatment flares could be higher. [See Warnings and Precautions (5.1).]

Table 5: Exacerbations of Hepatitis During Off-Treatment Follow-up, Subjects in Studies AI463022, AI463027, and AI463026

<table>
<thead>
<tr>
<th>Subjects with ALT Elevations &gt;10 x ULN and &gt;2 x Reference</th>
<th>BARACLUDE</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside-inhibitor-naïve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg-positive</td>
<td>4/174 (2%)</td>
<td>13/147 (9%)</td>
</tr>
<tr>
<td>HBeAg-negative</td>
<td>24/302 (8%)</td>
<td>30/270 (11%)</td>
</tr>
<tr>
<td>Lamivudine-refractory</td>
<td>6/52 (12%)</td>
<td>0/16</td>
</tr>
</tbody>
</table>

a Reference is the minimum of the baseline or last measurement at end of dosing. Median time to off-treatment exacerbation was 23 weeks for BARACLUDE-treated subjects and 10 weeks for lamivudine-treated subjects.
Table 6: Principal Analyses of Time to Adjudicated Events - Randomized Treated Subjects

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Number of Subjects with Events</th>
<th>Hazard Ratio [BARACLUDE:Non-ETV] (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall malignant neoplasm</td>
<td>331</td>
<td>337</td>
</tr>
<tr>
<td>Liver-related HBV disease progression</td>
<td>350</td>
<td>375</td>
</tr>
<tr>
<td>Death</td>
<td>238</td>
<td>264</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HCC malignant neoplasm</td>
<td>95</td>
<td>81</td>
</tr>
<tr>
<td>HCC</td>
<td>240</td>
<td>263</td>
</tr>
</tbody>
</table>

Analyses were stratified by geographic region and prior HBV nucleos(t)ide experience.

a 95.03% CI for overall malignant neoplasm, death, and liver-related HBV disease progression; 95% CI for non-HCC malignant neoplasm and HCC.
b One subject had a pre-treatment HCC event and was excluded from the analysis.
c Overall malignant neoplasm is a composite event of HCC or non-HCC malignant neoplasm.

Limitations of the study included population changes over the long-term follow-up period and more frequent post-randomization treatment changes in the non-ETV group. In addition, the study was underpowered to demonstrate a difference in the non-HCC malignancy rate because of the lower than expected background rate.

Adverse Reactions from Postmarketing Spontaneous Reports

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.


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 compete for 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 Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BARACLUDE during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Prospective pregnancy data from the APR are not sufficient to adequately assess the risk of birth defects, miscarriage or adverse maternal or fetal outcomes. Entecavir use during pregnancy has been evaluated in a limited number of individuals reported to the APR and the number of exposures to entecavir is insufficient to make a risk assessment compared to a reference population. The estimated background rate for major birth defects is 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15–20%.

In animal reproduction studies, no adverse developmental effects were observed with entecavir at clinically relevant exposures. No developmental toxicities were observed at systemic exposures (AUC) approximately 25 (rats) and 200 (rabbits) times the exposure at the maximum recommended human dose (MRHD) of 1 mg/day (see Data).

De novo Liver Disease

Study AI463048 was a randomized, open-label study of BARACLUDE 1 mg once daily versus adefovir dipivoxil 10 mg once daily for up to 48 weeks in adult subjects with chronic HBV infection and evidence of hepatic decompensation, defined as a Child-Turcotte-Pugh (CTP) score of 7 or higher [see Clinical Studies (14.1)]. Among the 102 subjects receiving BARACLUDE, the most common treatment-emergent adverse events of any severity, regardless of causality, occurring through Week 48 were peripheral edema (16%), ascites (15%), pyrexia (14%), hepatic encephalopathy (10%), and upper respiratory infection (10%). Clinical adverse reactions not listed in Table 3 that were observed through Week 48 include blood bicarbonate decreased (2%) and renal failure (<1%).

Eighteen of 102 (18%) subjects treated with BARACLUDE and 18/89 (20%) subjects treated with adefovir dipivoxil died during the first 48 weeks of therapy. The majority of deaths (11 in the BARACLUDE group and 16 in the adefovir dipivoxil group) were due to liver-related causes such as hepatic failure, hepatic encephalopathy, hepatorenal syndrome, and upper gastrointestinal hemorrhage. The rate of hepatocellular carcinoma (HCC) through Week 48 was 6% (6/102) for subjects treated with BARACLUDE and 8% (7/89) for subjects treated with adefovir dipivoxil. Five percent of subjects in either treatment arm discontinued therapy due to an adverse event through Week 48.

No subject in either treatment arm experienced an on-treatment hepatic flare (ALT >2 × baseline and >10 × ULN) through Week 48. Eleven of 102 (11%) subjects treated with BARACLUDE and 11/89 (13%) subjects treated with adefovir dipivoxil had a confirmed increase in serum creatinine of 0.5 mg/dl through Week 48.

HBV/HBV Co-infected

The safety profile of BARACLUDE 1 mg (n=51) in HBV/HBV co-infected subjects enrolled in Study AI463038 was similar to that of placebo (n=17) through 24 weeks of blinded treatment and similar to that seen in non-HIV infected subjects [see Warnings and Precautions (5.2)].

Liver Transplant Recipients

Among 65 subjects receiving BARACLUDE in an open-label, post-liver transplant trial [see Use in Specific Populations (8.8)], the frequency and nature of adverse events were consistent with those expected in subjects who have received a liver transplant and the known safety profile of BARACLUDE.

Clinical Trial Experience in Pediatric Subjects

The safety of BARACLUDE in pediatric subjects 2 to less than 18 years of age is based on two clinical trials in subjects with chronic HBV infection (one Phase 2 pharmacokinetic trial [AI463029] and one Phase 3 trial [AI463189]). These trials provided experience in 168 HBeAg-positive subjects treated with BARACLUDE for a median duration of 72 weeks. The adverse reactions observed in pediatric subjects who received treatment with BARACLUDE were consistent with those observed in clinical trials of BARACLUDE in adults. Adverse drug reactions reported in greater than 1% of pediatric subjects included abdominal pain, rash events, poor palatability ("product taste abnormal"), nausea, diarrhea, and vomiting.

6.2 Postmarketing Experience

Data from Long-Term Observational Study

Study AI463080 was a randomized, global, observational, open-label Phase 4 study to assess long-term risks and benefits of BARACLUDE (0.5 mg/day or 1 mg/day) treatment as compared to other standard-of-care HBV nucleos(t)ide analogues in subjects with chronic HBV infection.

A total of 12,378 patients were treated with BARACLUDE (n=6,216) or other HBV nucleos(t)ide treatment [non-entecavir (ETV)] (n=6,162). Patients were evaluated at baseline and subsequently every 6 months for up to 10 years. The principal clinical outcome events assessed during the study were overall malignant neoplasms, liver-related HBV disease progression, HCC, non-HCC malignant neoplasms, and death. The study showed that BARACLUDE was not significantly associated with an increased risk of malignant neoplasms compared to other standard-of-care HBV nucleos(t)ides, as assessed by either the composite endpoint of overall malignant neoplasms or the individual endpoint of non-HCC malignant neoplasms. The most commonly reported malignancy in both the BARACLUDE and non-ETV groups was HCC followed by gastrointestinal malignancies. The data also showed that long-term BARACLUDE use was not associated with a lower occurrence of HBV disease progression or a lower rate of death overall compared to other HBV nucleos(t)ides. The principal clinical outcome event assessments are shown in Table 6.
Data

8.2 Lactation

Risk Summary

It is not known whether BARACLUDE is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, entecavir was present in milk (see Data). The developmental and health benefits of breastfeeding should be considered along with the potential for adverse effects in the breastfed infant from BARACLUDE or from the underlying maternal condition.

8.3 Pediatric Use

BARACLUDE was evaluated in two clinical trials of pediatric subjects 2 years of age and older with HBeAg-positive chronic HBV infection and compensated liver disease. The exposure of BARACLUDE in nucleoside-inhibitor-treatment-naive and lamivudine-experienced pediatric subjects 2 years of age and older with HBeAg-positive chronic HBV infection and compensated liver disease receiving 0.015 mg/kg/day or 0.03 mg/kg/day (up to 1 mg once daily) was evaluated in Study A9363189. Safety and efficacy of the selected dose in treatment-naive pediatric subjects were confirmed in Study A9463189, a randomized, placebo-controlled treatment trial (see Indications and Usage (1), Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)).

There are limited data available on the use of BARACLUDE in lamivudine-experienced pediatric patients; BARACLUDE should be used in these patients only if the potential benefit justifies the potential risk to the child. Since some pediatric patients may require long-term or even lifetime management of chronic active hepatitis B, consideration should be given to the impact of BARACLUDE on future treatment options (see Microbiology (12.4)).

The efficacy and safety of BARACLUDE have not been established in patients less than 2 years of age. Use of BARACLUDE in this age group has not been evaluated because treatment of HBV in this age group is rarely required.

8.4 Pediatric Use

BARACLUDE was evaluated in two clinical trials of pediatric subjects 2 years of age and older with HBeAg-positive chronic HBV infection and compensated liver disease. The exposure of BARACLUDE in nucleoside-inhibitor-treatment-naive and lamivudine-experienced pediatric subjects 2 years of age and older with HBeAg-positive chronic HBV infection and compensated liver disease receiving 0.015 mg/kg/day or 0.03 mg/kg/day (up to 1 mg once daily) was evaluated in Study A9363189. Safety and efficacy of the selected dose in treatment-naive pediatric subjects were confirmed in Study A9463189, a randomized, placebo-controlled treatment trial (see Indications and Usage (1), Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)).

There are limited data available on the use of BARACLUDE in lamivudine-experienced pediatric patients; BARACLUDE should be used in these patients only if the potential benefit justifies the potential risk to the child. Since some pediatric patients may require long-term or even lifetime management of chronic active hepatitis B, consideration should be given to the impact of BARACLUDE on future treatment options (see Microbiology (12.4)).

The efficacy and safety of BARACLUDE have not been established in patients less than 2 years of age. Use of BARACLUDE in this age group has not been evaluated because treatment of HBV in this age group is rarely required.

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 from younger subjects. Entecavir is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)).

8.6 Racial/Ethnic Groups

There are no significant racial differences in entecavir pharmacokinetics. The safety and efficacy of BARACLUDE 0.5 mg once daily were assessed in a single-arm, open-label trial of HBeAg-negative or -positive, nucleoside-inhibitor-naive, Black/African American (n=40) and Hispanic (n=6) subjects with chronic HBV infection. In this trial, 76% of subjects were male, the mean age was 42 years, 57% were HBeAg-positive, the mean baseline HBV DNA was 7.0 log10 IU/mL, and the mean baseline ALT was 162 U/L. At Week 48 of treatment, 32 of 46 (70%) subjects had HBV DNA <50 IU/mL (approximately 300 copies/mL), 15 of 46 (67%) subjects had ALT normalization (<1 ULN), and 12 of 26 (46%) HBeAg-positive subjects had HBe seroconversion. Safety data were similar to those observed in the larger controlled clinical trials. Because of low enrollment, safety and efficacy have not been established in the US Hispanic population.

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 (2.4) and Clinical Pharmacology (12.3)).
BARACLUDE® (entecavir)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Entecavir is an antiviral drug against hepatitis B virus [see Microbiology (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 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 16%–20% [see Dosage and Administration (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 effect of age on the pharmacokinetics of entecavir was evaluated following a single 1 mg oral dose in healthy young and elderly volunteers.

**Hepatic Impairment:** The pharmacokinetics of entecavir following a single 1 mg dose were studied in adult subjects (without chronic hepatitis B virus infection) with moderate or severe hepatic impairment (Child-Turcotte-Pugh Class B or C). The pharmacokinetics of entecavir were similar between hepatically impaired and healthy control subjects; therefore, no dosage adjustment of BARACLUDE is recommended for patients with hepatic impairment. The pharmacokinetics of entecavir have not been studied in pediatric subjects with hepatic impairment.

**Post-liver transplant:** Limited data are available on the safety and efficacy of BARACLUDE in liver transplant recipients. In a small pilot study of entecavir use in HBV-infected liver transplant recipients on a stable dose of cyclosporine A (n=5) or tacrolimus (n=4), entecavir exposure was approximately 2-fold the exposure in healthy subjects with normal renal function. Altered renal function contributed to the increase in entecavir exposure in these subjects. The potential for pharmacokinetic interactions between entecavir and cyclosporine A or tacrolimus was not formally evaluated [see Use in Specific Populations (8.8)].

**Drug Interactions**
The metabolism of entecavir was evaluated in vitro and in vivo studies. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system.

At concentrations up to approximately 10,000-fold higher than those obtained in humans, entecavir inhibited none of the major human CYP450 enzymes 1A2, 2C9, 2C19, 2D6, 3A4, and 2B6. The pharmacokinetics of entecavir are unlikely to be affected by coadministration with agents that are either metabolized by, inhibit, or induce the CYP450 system.

**Mechanism of Action**
Entecavir, a deoxyguanosine 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 α, β, and δ and mitochondrial DNA polymerase γ with Ki values ranging from 18 to >160 μM.

**Antiviral Activity**
Entecavir inhibited HBV DNA synthesis (50% reduction, EC50) at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. The median EC50 value for entecavir against lamivudine-resistant HBV (rtL180M, rtM204V) was 0.026 μM (range 0.010–0.059 μM).

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. In HIV antiviral assays,

### Table 7: Pharmacokinetic Parameters in Pediatric Subjects

<table>
<thead>
<tr>
<th>Nucleoside-Inhibitor-NAïve</th>
<th>Lamivudine-Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=24</td>
<td>n=19</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td></td>
</tr>
<tr>
<td>(CV%)</td>
<td>6.31</td>
</tr>
<tr>
<td>(30)</td>
<td>14.48</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;Cmax&lt;/sub&gt; (ng•h/mL)</td>
<td>18.33</td>
</tr>
<tr>
<td>(CV%)</td>
<td>38.58</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>0.28</td>
</tr>
<tr>
<td>(CV%)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

\*Subjects received once-daily doses of 0.015 mg/kg up to a maximum of 0.5 mg.

\*Subjects received once-daily doses of 0.030 mg/kg up to a maximum of 1 mg.

**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 (2.4)].

### Table 8: 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>Unimpaired</td>
<td></td>
</tr>
<tr>
<td>n=6</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>8.1</td>
</tr>
<tr>
<td>(CV%)</td>
<td>14.48</td>
</tr>
<tr>
<td>&gt;50–&lt;80</td>
<td>27.9</td>
</tr>
<tr>
<td>(CV%)</td>
<td>40.3</td>
</tr>
<tr>
<td>Moderate</td>
<td>135.6</td>
</tr>
<tr>
<td>n=6</td>
<td>239.3</td>
</tr>
<tr>
<td>Severe</td>
<td>NA</td>
</tr>
<tr>
<td>Managed with Hemodialysis</td>
<td>NA</td>
</tr>
<tr>
<td>n=5</td>
<td>221.8</td>
</tr>
<tr>
<td>Severe</td>
<td>NA</td>
</tr>
<tr>
<td>Managed with CAPD</td>
<td></td>
</tr>
<tr>
<td>n=4</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{Cmax (ng/mL)}\) = maximum plasma concentration at steady state. \(\text{AUC (0–24) (ng•h/mL)}\) = area under the concentration-time curve (AUC) at steady state for the first 24 hours.

Following a single 1 mg dose of entecavir administered 2 hours before the hemodialysis session, hemodialysis removed approximately 13% of the entecavir dose over 4 hours. CAPD removed approximately 0.3% of the dose over 7 days [see Dosage and Administration (2.4)].

**Hepatic impairment:** The pharmacokinetics of entecavir following a single 1 mg dose were studied in adult subjects (without chronic hepatitis B virus infection) with moderate or severe hepatic impairment (Child-Turcotte-Pugh Class B or C). The pharmacokinetics of entecavir were similar between hepatically impaired and healthy control subjects; therefore, no dosage adjustment of BARACLUDE is recommended for patients with hepatic impairment. The pharmacokinetics of entecavir have not been studied in pediatric subjects with hepatic impairment.

**Post-liver transplant:** Limited data are available on the safety and efficacy of BARACLUDE in liver transplant recipients. In a small pilot study of entecavir use in HBV-infected liver transplant recipients on a stable dose of cyclosporine A (n=5) or tacrolimus (n=4), entecavir exposure was approximately 2-fold the exposure in healthy subjects with normal renal function. Altered renal function contributed to the increase in entecavir exposure in these subjects. The potential for pharmacokinetic interactions between entecavir and cyclosporine A or tacrolimus was not formally evaluated [see Use in Specific Populations (8.8)].
entecavir was not antagonistic to the cell culture anti-HIV activity of these six NRTIs or emtricitabine at concentrations greater than 100 times the 
\( C_{\text{50}} \) of entecavir using the 1 mg dose.

Arthritival Activity Against HIV

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

Resistance

In Cell Culture

In cell-based assays, 8- to 30-fold reductions in entecavir phenotypic sensitivity were observed for lamivudine-resistant strains. Further reductions (>70-fold) in entecavir phenotypic sensitivity required the presence of amino acid substitutions rtM204I/V with or without rtL80V, rtV173L, or rtL180M, which are associated with lamivudine and telbivudine resistance, as well as further decreased drug susceptibility to entecavir. The efficacy of entecavir against HBV harboring adefovir resistance-associated substitutions has not been established in clinical trials. HBV isolates from lamivudine-refractory subjects failing entecavir therapy were susceptible in cell culture to adefovir but remained resistant to lamivudine. Recombinant HBV genomes encoding adefovir resistance-associated substitutions at either rtA181V/G/T or rtM204I/V showed 1.1- to 0.3-fold shifts in sensitivity to entecavir in cell culture, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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. It is not known how predictive the results of rodent carcinogenicity studies may be for humans [see Adverse Reactions (6.2)]. 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 20 times those in male mice at exposures 10 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 20 times those in humans. Vascular tumors in female mice (hemangiosarcoma of ovaries and uterus and hemangiosarcoma 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 35 and 24 times those in humans. Skin fibromas were induced in females at exposures 4 times those in humans.

Mutagenesis

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.

Impairment of Fertility

In reproductive toxicology 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 rodents and dog toxicology studies, seminiferous tubal degeneration was observed at exposures 35 times or greater than those achieved in humans. No testicular changes were evident in monkeys.

14 CLINICAL STUDIES

14.1 Outcomes in Adults

At 48 Weeks

The safety and efficacy of BARACLUDE in adults were evaluated in three Phase 3 active-controlled trials. These studies included 1633 subjects 16 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 qDNA 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.

Nucleoside-inhibitor-naive Subjects with Compensated Liver Disease

HBsAg-positive: Study A643022 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 709 (of 715 randomized) nucleoside-inhibitor-naive subjects with chronic hepatitis B virus infection, compensated liver disease, and detectable HBsAg. The median 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

Baraclude® (entecavir)
BARACLUDE® (entecavir)

Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA as measured by Roche COBAS Amplicor® 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. Histologic Improvement (Knodell Scores)

Table 9: Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Nucleoside-Inhibitor-Naive Subjects in Studies AI463022 and AI463027

<table>
<thead>
<tr>
<th></th>
<th>Study AI463022 (HBeAg-Positive)</th>
<th>Study AI463027 (HBeAg-Negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic Improvement (Knodell Scores)</td>
<td>BARACLUDE</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>0.5 mg n=314</td>
<td>0.5 mg n=296</td>
<td>0.5 mg n=314</td>
</tr>
<tr>
<td>Improvementa</td>
<td>72%</td>
<td>62%</td>
</tr>
<tr>
<td>No improvement</td>
<td>21%</td>
<td>24%</td>
</tr>
<tr>
<td>Ishak Fibrosis Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvementa</td>
<td>35%</td>
<td>36%</td>
</tr>
<tr>
<td>No change</td>
<td>46%</td>
<td>40%</td>
</tr>
<tr>
<td>Worseningc</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Missing Week 48 biopsy</td>
<td>7%</td>
<td>14%</td>
</tr>
</tbody>
</table>

a Subjects with evaluable baseline histology (baseline Knodell Necroinflammatory Score ≥2).

b ≥2-point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.

c For Ishak Fibrosis Score, improvement = ≥1-point decrease from baseline and worsening = ≥1-point increase from baseline.

Table 10: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Nucleoside-Inhibitor-Naive Subjects in Studies AI463022 and AI463027

<table>
<thead>
<tr>
<th></th>
<th>Study AI463022 (HBeAg-Positive)</th>
<th>Study AI463027 (HBeAg-Negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNAa</td>
<td>BARACLUDE</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>0.5 mg n=254</td>
<td>0.5 mg n=255</td>
<td>0.5 mg n=254</td>
</tr>
<tr>
<td>Proportion undetectable (&lt;300 copies/mL)</td>
<td>67%</td>
<td>36%</td>
</tr>
<tr>
<td>Mean change from baseline (log10 copies/mL)</td>
<td>-6.86</td>
<td>-5.39</td>
</tr>
<tr>
<td>ALT normalization (&lt;1 × ULN)</td>
<td>68%</td>
<td>60%</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>21%</td>
<td>18%</td>
</tr>
</tbody>
</table>

a Roche COBAS Amplicor PCR assay [lower limit of quantification (LLOQ) = 300 copies/mL].

Histologic Improvement was independent of baseline levels of HBV DNA or ALT.

Table 11: Histologic Improvement (Knodell Scores)

<table>
<thead>
<tr>
<th></th>
<th>BARACLUDE</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvementa</td>
<td>55%</td>
<td>28%</td>
</tr>
<tr>
<td>No improvement</td>
<td>34%</td>
<td>57%</td>
</tr>
<tr>
<td>Ishak Fibrosis Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvementa</td>
<td>34%</td>
<td>16%</td>
</tr>
<tr>
<td>No change</td>
<td>44%</td>
<td>42%</td>
</tr>
<tr>
<td>Worseningc</td>
<td>11%</td>
<td>26%</td>
</tr>
<tr>
<td>Missing Week 48 biopsy</td>
<td>11%</td>
<td>16%</td>
</tr>
</tbody>
</table>

a Subjects with evaluable baseline histology (baseline Knodell Necroinflammatory Score ≥2).
b ≥2-point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.
c For Ishak Fibrosis Score, improvement = ≥1-point decrease from baseline and worsening = ≥1-point increase from baseline.

Table 12: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Lamivudine-Refractory Subjects in Study AI463026

<table>
<thead>
<tr>
<th></th>
<th>BARACLUDE</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNAa</td>
<td>Proportion undetectable (&lt;300 copies/mL)</td>
<td>19%</td>
</tr>
<tr>
<td>Mean change from baseline (log10 copies/mL)</td>
<td>-5.11</td>
<td>-0.48</td>
</tr>
<tr>
<td>ALT normalization (&lt;1 × ULN)</td>
<td>61%</td>
<td>15%</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>8%</td>
<td>3%</td>
</tr>
</tbody>
</table>

a Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).

Histologic Improvement was independent of baseline levels of HBV DNA or ALT.

Subjects with Decompensated Liver Disease

Study AI463048 was a randomized, open-label study of BARACLUDE 1 mg once daily versus adefovir dipivoxil 10 mg once daily in 191 (of 195 randomized) adult subjects with HBeAg-positive or -negative chronic HBV infection and evidence of hepatic decompensation, defined as a Child-Turcotte-Pugh (CTP) score of 7 or higher. Subjects were either HBV-treatment-naive or previously treated, predominantly with lamivudine or interferon-α.

In Study AI463048, 100 subjects were randomized to treatment with BARACLUDE and 91 subjects to treatment with adefovir dipivoxil. Two subjects randomized to treatment with adefovir dipivoxil actually received treatment with BARACLUDE for the duration of the study. The mean age of subjects was 52 years, 74% were male, 54% were Asian, 33% were Caucasian, and 5% were Black/African American. At baseline, subjects had a mean Knodell Necroinflammatory Score of 6.5, mean serum HBV DNA as measured by Roche COBAS Amplicor PCR assay was 9.36 log10 copies/mL, and mean serum ALT level was 128 U/L. Paired, adequate liver biopsy samples were available for 67% of subjects.

Table 13: Selected Endpoints at Week 48, Subjects with Decompensated Liver Disease, Study AI463048

<table>
<thead>
<tr>
<th></th>
<th>BARACLUDE</th>
<th>Adefovir Dipivoxil</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNAa</td>
<td>Proportion undetectable (&lt;300 copies/mL)</td>
<td>57%</td>
</tr>
<tr>
<td>Stable or improved CTP scoreb</td>
<td>61%</td>
<td>67%</td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>5%</td>
<td>0</td>
</tr>
<tr>
<td>Normalization of ALT (&lt;1 × ULN)c</td>
<td>49/78 (63%)</td>
<td>33/71 (46%)</td>
</tr>
</tbody>
</table>

a Endpoints were analyzed using intention-to-treat (ITT) method, treated subjects as randomized.
b Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).
c Defined as decrease or no change from baseline in CTP score.

d Denominator is subjects with abnormal values at baseline. ULN—upper limit of normal.
Subjects Co-infected with HIV and HBV

Study A463038 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 add 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 when 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 HBsAg-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 14. There are no data in patients with HIV/HBV co-infection who have not received prior blinded 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 14: Virologic and Biochemical Endpoints at Week 24, Study A463038

<table>
<thead>
<tr>
<th>BARACLUDE 1 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=51</td>
<td>n=17</td>
</tr>
<tr>
<td><strong>HBV DNA</strong></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 (≤1 × ULN)</td>
<td>34%</td>
</tr>
</tbody>
</table>

All subjects also received a lamivudine-containing HAART regimen.

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, and 37% of subjects with (Week 48), 8% of subjects had HBV DNA <300 copies/mL by PCR, the mean change from baseline HBV DNA level by PCR of 9.13 log_{10} copies/mL. Ninety-nine percent of subjects 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 HBsAg-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 14. There are no data in patients with HIV/HBV co-infection who have not received prior blinded 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)].

Among lamivudine-refractory subjects (Study A463026), 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%) subjects had ALT ≤1 × ULN, and 8 (10%) subjects demonstrated HBsAg seroconversion at the end of dosing.

14.2 Outcomes in Pediatric Subjects

The pharmacokinetics, safety and antiviral activity of BARACLUDE in pediatric subjects were initially assessed in Study A463028. Twenty-four treatment-naïve and 19 lamivudine-experienced HBsAg-positive pediatric subjects 2 to less than 18 years of age with compensated chronic hepatitis B virus infection and elevated ALT were treated with BARACLUDE 0.015 mg/kg (up to 0.5 mg) or 0.03 mg/kg (up to 1 mg) once daily. Fifty-eight percent (14/24) of treatment-naïve subjects and 47% (9/19) of lamivudine-experienced subjects achieved HBV DNA <50 IU/mL at Week 48 and ALT normalized in 83% (20/24) of treatment-naïve and 95% (18/19) of lamivudine-experienced subjects. Safety and antiviral efficacy were confirmed in Study A463189, a study of BARACLUDE among 180 nucleoside-inhibitor-treatment-naïve pediatric subjects 2 to less than 18 years of age with HBsAg-positive chronic hepatitis B virus infection, compensated liver disease, and elevated ALT. Subjects were randomized 2:1 to receive blinded treatment with BARACLUDE 0.015 mg/kg up to 0.5 mg/day (N=120) or placebo (N=60). The randomization was stratified by age group (2 to 6 years; >6 to 12 years; and >12 to <18 years). Baseline demographics and HIV disease characteristics were comparable between the 2 treatment arms and across age cohorts. At study entry, the mean HBV DNA was 8.1 log_{10} IU/mL and mean ALT was 103 U/L. The primary efficacy endpoint was a composite of HBsAg seroconversion and serum HBV DNA <50 IU/mL at Week 48 as defined in the first 123 subjects reaching 48 weeks of blinded treatment. Twenty-four percent (20/82) of subjects in the BARACLUDE-treated group and 2% (1/41) of subjects in the placebo-treated group met the primary endpoint. Forty-six percent (38/82) of BARACLUDE-treated subjects and 2% (1/41) of placebo-treated subjects achieved HBV DNA <50 IU/mL at Week 48. ALT normalization occurred in 67% (55/82) of BARACLUDE-treated subjects and 22% (9/41) of placebo-treated subjects; 24% (20/82) of BARACLUDE-treated subjects and 12% (5/41) of placebo-treated subjects had HBsAg seroconversion.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 Strength and Dosage Form</th>
<th>Description</th>
<th>Quantity</th>
<th>NDC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg film-coated tablet</td>
<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>1 mg film-coated tablet</td>
<td>Pink, triangular-shaped tablet, debossed with “BMS” on one side and “1612” on the other side.</td>
<td>30 tablets</td>
<td>0003-1612-12</td>
</tr>
<tr>
<td>0.05 mg/mL oral solution</td>
<td>Ready-to-use, orange-flavored, clear, colorless to pale yellow, aqueous solution in a 200 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 0.5 mL increments up to 10 mL.

Storage

BARACLUDE Tablets should be stored in a tightly closed container at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Store in the outer carton to protect from light.

BARACLUDE Oral Solution should be stored in the outer carton at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 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 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Severe Acute Exacerbation of Hepatitis after Discontinuation of Treatment

Inform patients that discontinuation of anti-hepatitis B therapy, including BARACLUDE, may result in severe acute exacerbations of hepatitis B. Advise the patient not to discontinue BARACLUDE without first informing their healthcare provider [see Warnings and Precautions (5.1)].

Risk of Development of HIV-1 Resistance in Patients with HIV-1 Coinfection

Inform patients that if they have or develop HIV infection and are not receiving effective HIV treatment, BARACLUDE may increase the risk of development of resistance to HIV medication [see Warnings and Precautions (5.2)].
Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to BARACLUDE. Advise patients to contact their healthcare provider immediately and stop BARACLUDE if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity [see Warnings and Precautions (5.3)].

Missed Dosage

Inform patients that it is important to take BARACLUDE on a regular dosing schedule on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal) and to avoid missing doses as it can result in development of resistance [see Dosage and Administration (2.1)].

Treatment Duration

Advise patients that in the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. The relationship between response and long-term prevention of outcomes such as hepatocellular carcinoma is not known.

Instructions for Use

Inform patients using the oral solution 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. Some patients may find it difficult to accurately measure the prescribed dose using the provided dosing spoon; therefore, patients/caregivers should refer to the steps in the Patient Information section that demonstrate the correct technique of using the provided dosing spoon to measure the prescribed BARACLUDE dose.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BARACLUDE during pregnancy [see Use in Specific Populations (8.1)].
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 (HBV) 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.
Baracude® (Entecavir)

- 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 Baracude, for a long time.

What is Baracude?

Baracude is a prescription medicine used to treat chronic hepatitis B virus (HBV) in adults and children 2 years of age and older who have active liver disease.

- Baracude will not cure HBV.
- Baracude may lower the amount of HBV in the body.
- Baracude may lower the ability of HBV to multiply and infect new liver cells.
- Baracude may improve the condition of your liver.
- It is not known whether Baracude 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 Baracude is safe and effective for use in children less than 2 years of age.

What should I tell my healthcare provider before taking Baracude?

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

- have kidney problems. Your Baracude 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 Baracude. These people may have less benefit from treatment with Baracude 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 Baracude will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant. Antiretroviral Pregnancy Registry. If you take Baracude while you are pregnant, talk to your healthcare provider about how you can take part in the Baracude Antiretroviral Pregnancy Registry. The purpose of the pregnancy registry is to collect information about the health of you and your baby.
- are breastfeeding or plan to breastfeed. It is not known if Baracude can pass into your breast milk. You and your healthcare provider should decide if you will take Baracude or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you have taken a medicine to treat HBV in the past.

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 Baracude?

- Take Baracude exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much Baracude to take.
- Your healthcare provider will tell you when and how often to take Baracude.
- Take Baracude 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, or giving it to your child, carefully measure the dose with the dosing spoon provided, as follows:

  • Hold the dosing spoon in an upright (vertical) position and slowly fill it to the measurement line on the dosing spoon that is the same as the prescribed dose. Bring the dosing spoon to eye level to be sure that the level of the BARACLUDE Oral Solution is at the correct measurement line (see Figure 1).

  • With the dosing spoon at eye level, holding it with the measurement lines facing you, check that it has been filled to the correct measurement line. The top of the BARACLUDE Oral Solution in the dosing spoon will look curved, not flat. Measure the dose of BARACLUDE Oral Solution at the bottom of the curve. Your dose of BARACLUDE Oral Solution is measured correctly when the bottom of the curve is lined up with the measurement line of the prescribed dose. As an example, Figure 2 shows the right way to measure a 5 mL dose of BARACLUDE (see Figure 2).

  • BARACLUDE Oral Solution should be swallowed directly from the dosing spoon.

  • BARACLUDE Oral Solution should not be mixed with water or any other liquid.

  • After each use, rinse the dosing spoon with water and allow it to air dry.

  • If you lose the dosing 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 miss a dose of 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.

• 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.
How should I store BARACLUDE?

- Store BARACLUDE Tablets or Oral Solution at room temperature, between 68°F and 77°F (20°C and 25°C).
- Keep BARACLUDE Tablets in a tightly closed container.
- Store BARACLUDE Tablets or BARACLUDE Oral Solution in the original carton, and keep the carton 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 health professionals.

For more information, go to www.Baraclude.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.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

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

Revised: August 2015

686US1903784-01-01 11/19

Bristol-Myers Squibb