HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BARACLUDE safely and effectively. See full prescribing information for BARACLUDE.

BARACLUDE® (entecavir) Tablets
BARACLUDE® (entecavir) Oral Solution
Initial U.S. Approval: 2005

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)**

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

----------DOSAGE AND ADMINISTRATION----------
- Nucleoside-treatment-naïve (≥16 years old): 0.5 mg once daily. (2.1)
- Lamivudine-refractory or known lamivudine or telbivudine resistance mutations (≥16 years old): 1 mg once daily. (2.1)
- Renal impairment: Dosage adjustment is recommended if creatinine clearance is less than 50 mL/min. (2.2)
- BARACLUDE should be administered on an empty stomach. (2)

----------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 07/2009

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FULL PRESCRIBING INFORMATION

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, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted [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 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 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 either 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 with compensated liver disease [see *Clinical Studies (14)*].

- Limited data are available in adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy [see *Warnings and Precautions (5.2)* and *Clinical Studies (14)*].
- BARACLUDE has not been evaluated in patients with decompensated liver disease.

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

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/V, or rtV173L is 1 mg once daily.

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 1: Recommended Dosage of BARACLUDE in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Usual Dose (0.5 mg)	Lamivudine-Refractory (1 mg)
≥50	0.5 mg once daily	1 mg once daily
30 to <50	0.25 mg once daily[a] **OR** 0.5 mg every 48 hours	0.5 mg once daily **OR** 1 mg every 48 hours
10 to <30	0.15 mg once daily[a] **OR** 0.5 mg every 72 hours	0.3 mg once daily[a] **OR** 1 mg every 72 hours
<10 Hemodialysis[b] or CAPD	0.05 mg once daily[a] **OR** 0.5 mg every 7 days	0.1 mg once daily[a] **OR** 1 mg every 7 days

[a] For doses less than 0.5 mg, BARACLUDE Oral Solution is recommended.

[b] 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 “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.

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.

Assessment of adverse reactions is based on four studies (AI463014, AI463022, AI463026, and AI463027) in which 1720 subjects with chronic hepatitis B virus infection received double-blind treatment with BARACLUDE 0.5 mg/day (n=679), BARACLUDE 1 mg/day (n=183), or lamivudine (n=858) 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 safety profile of BARACLUDE 1 mg (n=51) in HIV/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)*].

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-severe 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[a] of Moderate-Severe Intensity (Grades 2-4) Reported in Four Entecavir Clinical Trials Through 2 Years

	Nucleoside-Naïve[b]		Lamivudine-Refractory[c]	
Body System/ Adverse Reaction	**BARACLUDE 0.5 mg n=679**	**Lamivudine 100 mg n=668**	**BARACLUDE 1 mg n=183**	**Lamivudine 100 mg n=190**
Any Grade 2-4 adverse reaction[a]	15%	18%	22%	23%
Gastrointestinal				
Diarrhea	<1%	0	1%	0
Dyspepsia	<1%	<1%	1%	0
Nausea	<1%	<1%	<1%	2%
Vomiting	<1%	<1%	<1%	0
General				
Fatigue	1%	1%	3%	3%
Nervous System				
Headache	2%	2%	4%	1%
Dizziness	<1%	<1%	0	1%
Somnolence	<1%	<1%	0	0
Psychiatric				
Insomnia	<1%	<1%	0	<1%

[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 3.

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

	Nucleoside-Naïve[b]		Lamivudine-Refractory[c]	
Test	BARACLUDE 0.5 mg n=679	Lamivudine 100 mg n=668	BARACLUDE 1 mg n=183	Lamivudine 100 mg n=190
Any Grade 3-4 laboratory abnormality[d]	35%	36%	37%	45%
ALT >10 X ULN and >2 X baseline	2%	4%	2%	11%
ALT >5.0 X ULN	11%	16%	12%	24%
Albumin <2.5 g/dL	<1%	<1%	0	2%
Total bilirubin >2.5 X ULN	2%	2%	3%	2%
Lipase ≥2.1 X ULN	7%	6%	7%	7%
Creatinine >3.0 X ULN	0	0	0	0
Confirmed creatinine increase ≥0.5 mg/dL	1%	1%	2%	1%
Hyperglycemia, fasting >250 mg/dL	2%	1%	3%	1%
Glycosuria[e]	4%	3%	4%	6%
Hematuria[f]	9%	10%	9%	6%
Platelets <50,000/mm^3	<1%	<1%	<1%	<1%

[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 $\log_{10}$/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 [see also *Warnings and Precautions (5.1)*]

An exacerbation of hepatitis or ALT flare was defined as ALT greater than 10 times ULN and greater than 2 times the subject's reference level (minimum of the baseline or last measurement at end of dosing). For all subjects who discontinued treatment (regardless of reason), Table 4 presents the proportion of subjects in each study who experienced post-treatment ALT flares. In these studies, 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.

Table 4: Exacerbations of Hepatitis During Off-Treatment Follow-up, Subjects in Studies AI463022, AI463027, and AI463026

	Subjects with ALT Elevations >10 X ULN and >2 X Reference[a]	
	BARACLUDE	**Lamivudine**
Nucleoside-naïve		
HBeAg-positive	4/174 (2%)	13/147 (9%)
HBeAg-negative	24/302 (8%)	30/270 (11%)
Lamivudine-refractory	6/52 (12%)	0/16

[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.

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.

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 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 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 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 (2.2)*].

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)*].

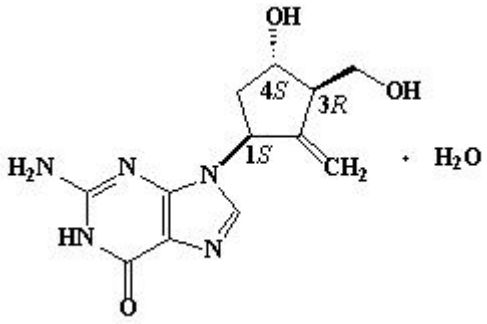
10 OVERDOSAGE

There is limited experience of entecavir overdosage 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 tradename for entecavir, a guanosine nucleoside analogue with selective activity against HBV. The chemical name for entecavir is 2-amino-1,9-dihydro-9-[(*1S,3R,4S*)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6*H*-purin-6-one, monohydrate. Its molecular formula is $C_{12}H_{15}N_5O_3 \cdot H_2O$, 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° ± 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, povidone, 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, C_{max} 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, C_{max} at steady state was 4.2 ng/mL and trough plasma concentration (C_{trough}) was 0.3 ng/mL. For a 1-mg oral dose, C_{max} was 8.2 ng/mL and C_{trough} 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 C_{max} of 44%-46%, and a decrease in AUC of 18%-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 ^{14}C-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)*].

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

	Renal Function Group					
	Baseline Creatinine Clearance (mL/min)					
	Unimpaired >80	Mild >50-≤80	Moderate 30-50	Severe <30	Severe Managed with Hemodialysis[a]	Severe Managed with CAPD
	n=6	n=6	n=6	n=6	n=6	n=4
C_{max} (ng/mL) (CV%)	8.1 (30.7)	10.4 (37.2)	10.5 (22.7)	15.3 (33.8)	15.4 (56.4)	16.6 (29.7)
$AUC_{(0-T)}$ (ng•h/mL) (CV)	27.9 (25.6)	51.5 (22.8)	69.5 (22.7)	145.7 (31.5)	233.9 (28.4)	221.8 (11.6)
CLR (mL/min) (SD)	383.2 (101.8)	197.9 (78.1)	135.6 (31.6)	40.3 (10.1)	NA	NA
CLT/F (mL/min) (SD)	588.1 (153.7)	309.2 (62.6)	226.3 (60.1)	100.6 (29.1)	50.6 (16.5)	35.7 (19.6)

[a] Dosed immediately following hemodialysis.
CLR = renal clearance; CLT/F = apparent oral clearance.

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 (2.2)*].

Hepatic impairment: The pharmacokinetics of entecavir following a single 1-mg dose were studied in subjects (without chronic hepatitis B virus infection) with moderate or severe hepatic impairment (Child-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.

Post-liver transplant: The safety and efficacy of BARACLUDE in liver transplant recipients are unknown. However, 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 (8.7)*].

Drug Interactions

The metabolism of entecavir was evaluated in *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, 2B6, and 2E1. At concentrations up to approximately 340-fold higher than those observed in humans, entecavir did not induce the human CYP450 enzymes 1A2, 2C9, 2C19, 3A4, 3A5, 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. Likewise, the pharmacokinetics of known CYP substrates are unlikely to be affected by coadministration of entecavir.

The steady-state pharmacokinetics of entecavir and coadministered drug were not altered in interaction studies of entecavir with lamivudine, adefovir dipivoxil, and tenofovir disoproxil fumarate [see *Drug Interactions (7)*].

12.4 Microbiology

Mechanism of Action

Entecavir, a guanosine nucleoside analogue with activity against HBV polymerase, 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 polymerase (reverse transcriptase, rt): (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 K_i values ranging from 18 to >160 μM.

Antiviral Activity

Entecavir inhibited HBV DNA synthesis (50% reduction, EC_{50}) at a concentration of 0.004 μM 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 μM (range 0.010-0.059 μM).

The coadministration of HIV 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, 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_{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 >10 μM; the lower EC_{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 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 required the presence of amino acid substitutions rtM204I/V with or without rtL180M along with additional substitutions at residues rtT184, rtS202, or rtM250, or a combination of these substitutions with or without an rtI169 substitution in the HBV polymerase.

Clinical Studies

Nucleoside-naïve 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-naïve 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 = <1%), and 1 of them experienced virologic rebound (≥1 $\log_{10}$ increase above nadir). In addition, emerging amino acid substitutions at rtM204I/V and rtL180M, rtL80I, or rtV173L, which conferred decreased phenotypic susceptibility to entecavir in the absence of rtT184, rtS202, or rtM250 changes, were detected in the HBV of 3 subjects (3/562 = <1%) 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 rollover study. Complete response for HBeAg-positive was <0.7 MEq/mL (approximately 7 x 10^5 copies/mL) serum HBV DNA and HBeAg loss and, for HBeAg-negative was <0.7 MEq/mL HBV DNA and ALT normalization. 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 rtT184, rtS202, or rtM250 entecavir resistance-associated substitutions (in the presence of rtM204V and rtL180M substitutions) at Weeks 48, 96, 144, 192, 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 lamivudine-refractory HBV (AI463026, AI463014, AI463015, and rollover study AI463901). By Week 96, resistance-associated amino acid substitutions at rtS202, rtT184, or rtM250, with or without rtI169 changes, in the presence of amino acid substitutions rtM204I/V with or without rtL180M, rtL80V, or rtV173L/M emerged in the HBV from 22 subjects (22/190 = 12%), 16 of whom experienced virologic rebound (≥1 $\log_{10}$ 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 rtM204I/V and rtL180M, rtL80V, or rtV173L/M. For isolates from subjects who experienced virologic rebound with the emergence of resistance substitutions (n=19), the median fold-change in entecavir EC_{50} values from reference was 19-fold at baseline and 106-fold at the time of virologic rebound. For subjects who continued treatment beyond 48 weeks, 40% (31/77) had HBV DNA <300 copies/mL at end of dosing (up to 96 weeks).

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 subjects, 80 subjects entered the

long-term follow-up study and were evaluated for entecavir resistance. By Weeks 144, 192, and 240 (including end of dosing), 34% (27/80), 35% (28/80), and 36% (29/80), respectively, attained HBV DNA <300 copies/mL. The cumulative probability of developing rtT184, rtS202, or rtM250 entecavir resistance-associated substitutions (in the presence of rtM204I/V with or without rtL180M substitutions) at Weeks 48, 96, 144, 192, and 240 was 6.2%, 15%, 36.3%, 46.6%, and 51.5%, respectively. The HBV of 6 subjects developed rtA181C/G/S/T amino acid substitutions while receiving entecavir, and of these, 4 developed entecavir resistance-associated substitutions at rtT184, rtS202, or rtM250 and 1 had an rtT184S substitution at baseline. Of 7 subjects whose HBV had an rtA181 substitution at baseline, 2 also had substitutions at rtT184, rtS202, or rtM250 at baseline and another 2 developed them while on treatment with entecavir.

Cross-resistance

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, entecavir had 8- to 30-fold less inhibition of HBV DNA synthesis for HBV containing lamivudine and telbivudine resistance substitutions rtM204I/V with or without rtL180M than for wild-type HBV. Substitutions rtM204I/V with or without rtL180M, rtL80I/V, or rtV173L, which are associated with lamivudine and telbivudine resistance, also confer decreased phenotypic 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 rtN236T or rtA181V had 0.3- and 1.1-fold shifts in susceptibility to entecavir in cell culture, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 female mice (hemangiomas of ovaries and uterus and hemangiosarcomas 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.

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 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 rodent and dog toxicology studies, seminiferous tubular 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 at 48 Weeks

The safety and efficacy of BARACLUDE 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 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 68 subjects co-infected with HBV and HIV.

Nucleoside-naïve subjects with compensated liver disease

HBeAg-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 in 709 (of 715 randomized) nucleoside-naïve subjects with chronic hepatitis B virus infection and detectable HBeAg. 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 Amplicor® PCR assay was 9.66 $\log_{10}$ copies/mL, and mean serum ALT level was 143 U/L. Paired, adequate liver biopsy samples were available for 89% of subjects.

HBeAg-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-naïve subjects with HBeAg-negative (HBeAb-positive) chronic hepatitis B virus infection. 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 Amplicor PCR assay was 7.58 $\log_{10}$ copies/mL, and mean serum ALT level was 142 U/L. Paired, adequate liver biopsy samples were available for 88% of subjects.

In Studies AI463022 and AI463027, BARACLUDE was superior to lamivudine on the primary efficacy endpoint of Histologic Improvement, defined as a 2-point or greater reduction in Knodell Necroinflammatory Score with no worsening in Knodell Fibrosis Score at Week 48, and on the secondary efficacy measures of reduction in viral load and ALT normalization. Histologic Improvement and change in Ishak Fibrosis Score are shown in Table 6. Selected virologic, biochemical, and serologic outcome measures are shown in Table 7.

Table 6: Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Nucleoside-Naïve Subjects in Studies AI463022 and AI463027

	Study AI463022 (HBeAg-Positive)		Study AI463027 (HBeAg-Negative)	
	BARACLUDE 0.5 mg n=314[a]	**Lamivudine 100 mg n=314[a]**	**BARACLUDE 0.5 mg n=296[a]**	**Lamivudine 100 mg n=287[a]**
Histologic Improvement (Knodell Scores)				
Improvement[b]	72%*	62%	70%*	61%
No improvement	21%	24%	19%	26%
Ishak Fibrosis Score				
Improvement[c]	39%	35%	36%	38%
No change	46%	40%	41%	34%
Worsening[c]	8%	10%	12%	15%
Missing Week 48 biopsy	7%	14%	10%	13%

[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.

* $p<0.05$

Table 7: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Nucleoside-Naïve Subjects in Studies AI463022 and AI463027

	Study AI463022 (HBeAg-Positive)		Study AI463027 (HBeAg-Negative)	
	BARACLUDE 0.5 mg n=354	**Lamivudine 100 mg n=355**	**BARACLUDE 0.5 mg n=325**	**Lamivudine 100 mg n=313**
HBV DNA[a]				
Proportion undetectable (<300 copies/mL)	67%*	36%	90%*	72%
Mean change from baseline (log_{10} copies/mL)	-6.86*	-5.39	-5.04*	-4.53
ALT normalization (≤1 X ULN)	68%*	60%	78%*	71%
HBeAg seroconversion	21%	18%	NA	NA

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

* $p<0.05$

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

Lamivudine-refractory subjects

Study AI463026 was a multinational, randomized, double-blind study of BARACLUDE in 286 (of 293 randomized) subjects with lamivudine-refractory chronic hepatitis B virus infection. Subjects receiving lamivudine at study entry either switched to BARACLUDE 1 mg once daily (with neither a washout nor an overlap period) or continued on lamivudine 100 mg for a minimum of 52 weeks. The mean age of subjects was 39 years, 76% were male, 37% were Asian, 62% were Caucasian, and 52% had previously received interferon-α. The mean duration of prior lamivudine therapy was 2.7 years, and 85% had lamivudine resistance mutations at baseline by an investigational line probe assay. 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 $\log_{10}$ copies/mL, and mean serum ALT level was 128 U/L. Paired, adequate liver biopsy samples were available for 87% of subjects.

BARACLUDE was superior to lamivudine on a primary endpoint of Histologic Improvement (using the Knodell Score at Week 48). These results and change in Ishak Fibrosis Score are shown in Table 8. Table 9 shows selected virologic, biochemical, and serologic endpoints.

Table 8: Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Lamivudine-Refractory Subjects in Study AI463026

	BARACLUDE 1 mg n=124 [a]	**Lamivudine 100 mg n=116** [a]
Histologic Improvement (Knodell Scores)		
Improvement[b]	55%*	28%
No improvement	34%	57%
Ishak Fibrosis Score		
Improvement[c]	34%*	16%
No change	44%	42%
Worsening[c]	11%	26%
Missing Week 48 biopsy	11%	16%

[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.

* $p<0.01$

Table 9: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Lamivudine-Refractory Subjects in Study AI463026

	BARACLUDE 1 mg n=141	Lamivudine 100 mg n=145
HBV DNA[a]		
Proportion undetectable (<300 copies/mL)	19%*	1%
Mean change from baseline (log_{10} copies/mL)	-5.11*	-0.48
ALT normalization (≤1 X ULN)	61%*	15%
HBeAg seroconversion	8%	3%

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

* p<0.0001

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

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 AI463022), 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.

Among nucleoside-naïve, HBeAg-positive subjects, 74 (21%) BARACLUDE subjects and 67 (19%) lamivudine subjects met the definition of response at Week 48, discontinued study drugs, and were followed off treatment for 24 weeks. Among BARACLUDE responders, 26 (35%) subjects had HBV DNA <300 copies/mL, 55 (74%) subjects had ALT ≤1 X ULN, and 56 (76%) subjects sustained HBeAg seroconversion at the end of follow-up. Among lamivudine responders, 20 (30%) subjects had HBV DNA <300 copies/mL, 41 (61%) subjects had ALT ≤1 X ULN, and 47 (70%) subjects sustained HBeAg seroconversion at the end of follow-up.

Among nucleoside-naïve, HBeAg-negative subjects (Study AI463027), 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).

Among nucleoside-naïve, HBeAg-negative subjects, 275 (85%) BARACLUDE subjects and 245 (78%) lamivudine subjects met the definition of response at Week 48, discontinued study drugs, and were followed off treatment for 24 weeks. In this cohort, very few subjects in each treatment arm had HBV DNA <300 copies/mL by PCR at the end of follow-up. At the end of follow-up, 126 (46%) BARACLUDE subjects and 84 (34%) lamivudine subjects had ALT ≤1 X ULN.

Lamivudine-refractory subjects: Among lamivudine-refractory subjects (Study AI463026), 77 (55%) BARACLUDE-treated subjects and 3 (2%) lamivudine 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 X ULN, and 8 (10%) subjects demonstrated HBeAg seroconversion at the end of dosing.

14.3 Special Populations

Patients Co-infected with HIV and HBV

Study AI463038 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

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 10. 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 10: Virologic and Biochemical Endpoints at Week 24, Study AI463038

	BARACLUDE 1 mg[a] n=51	**Placebo[a] n=17**
HBV DNA[b]		
Proportion undetectable (<300 copies/mL)	6%	0
Mean change from baseline ($\log_{10}$ copies/mL)	-3.65*	+0.11
ALT normalization (≤1 X ULN)	34%[c]	8%[c]

[a] All subjects also received a lamivudine-containing HAART regimen.

[b] Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).

[c] Percentage of subjects with abnormal ALT (>1 X ULN) at baseline who achieved ALT normalization (n=35 for BARACLUDE and n=12 for placebo).

* $p<0.0001$

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 abnormal ALT at baseline had ALT normalization (≤1 X ULN).

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:

Product Strength and Dosage Form	Description	Quantity	NDC Number
0.5-mg film-coated tablet	White to off-white, triangular-shaped tablet, debossed with "BMS" on one side and "1611" on the other side.	30 tablets	0003-1611-12
		90 tablets	0003-1611-13
1.0-mg film-coated tablet	Pink, triangular-shaped tablet, debossed with "BMS" on one side and "1612" on the other side.	30 tablets	0003-1612-12
0.05-mg/mL oral solution	Ready-to-use, orange-flavored, clear, colorless to pale yellow aqueous solution in a 260-mL bottle.	210 mL	0003-1614-12

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 PATIENT COUNSELING INFORMATION

See *FDA-approved Patient Labeling (17.4)*.

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.

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.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

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17.4 FDA-approved Patient Labeling

Baraclude® (BEAR ah klude)
(generic name = **entecavir**)
Tablets and Oral Solution

Read the Patient Information that comes with BARACLUDE before you start taking it 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 or become very serious if you stop 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 will need to monitor your health and do regular blood tests to check your liver if you stop BARACLUDE. Tell your healthcare provider right away about any new or unusual symptoms that you notice after you stop taking BARACLUDE.

2. **If you have or get HIV (human immunodeficiency virus) infection be sure to discuss your treatment with your doctor.** If you are taking BARACLUDE to treat chronic hepatitis B and are not taking medicines for your HIV at the same time, some HIV treatments that you take in the future may be less likely to work. You are advised to get an HIV test before you start taking BARACLUDE and anytime after that when there is a chance you were exposed to HIV. BARACLUDE will not help your HIV infection.
3. **Some people who have taken medicines like BARACLUDE (a nucleoside analogue) have developed a serious condition called lactic acidosis** (buildup of an acid in the blood). Lactic acidosis is a serious medical emergency that can lead to death. Lactic acidosis must be treated in the hospital. **Call your healthcare provider right away if you get any of the following signs 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. **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). **Call your healthcare provider right away if you get any of the following signs 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.

What is BARACLUDE?

BARACLUDE is a prescription medicine used for chronic infection with hepatitis B virus (HBV) in adults who also 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 important to stay under your healthcare provider's care while taking BARACLUDE. 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.

Does BARACLUDE lower the risk of passing HBV to others?

BARACLUDE does not stop you from spreading 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.

Who should not take BARACLUDE?

Do not take BARACLUDE if you are allergic to any of its ingredients. The active ingredient in BARACLUDE is entecavir. See the end of this leaflet for a complete list of ingredients in BARACLUDE. Tell your healthcare provider if you think you have had an allergic reaction to any of these ingredients.

BARACLUDE has not been studied in children and is not recommended for anyone less than 16 years old.

What should I tell my healthcare provider before I take BARACLUDE?

Tell your healthcare provider about all of your medical conditions, including if you:

- **have kidney problems.** Your BARACLUDE dose or dose schedule may need to be adjusted.
- **are pregnant or planning to become pregnant.** It is not known if BARACLUDE is safe to use during pregnancy. It is not known whether BARACLUDE helps prevent a pregnant mother from passing HBV to her baby. You and your healthcare provider will need to decide if BARACLUDE is right for you. If you use BARACLUDE while you are pregnant, talk to your healthcare provider about the BARACLUDE Pregnancy Registry.
- **are breast-feeding.** It is not known if BARACLUDE can pass into your breast milk or if it can harm your baby. Do not breast-feed if you are taking BARACLUDE.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. BARACLUDE may interact with other medicines that leave the body through the kidneys.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist.

How should I take BARACLUDE?

- Take BARACLUDE exactly as prescribed. Your healthcare provider will tell you how much BARACLUDE to take. Your dose will depend on whether you have been treated for HBV infection before and what medicine you took. The usual dose of BARACLUDE Tablets is either 0.5 mg (one white tablet) or 1 mg (one pink tablet) once daily by mouth. The usual dose of BARACLUDE Oral Solution is either 10 mL or 20 mL once daily by mouth. Your dose may be lower or you may take BARACLUDE less often than once a day if you have kidney problems.
- **Take BARACLUDE once a day on an empty stomach** to help it work better. Empty stomach means at least 2 hours after a meal and at least 2 hours before the next meal. To help you remember to take your BARACLUDE, try to take it at the same time each day.
- If you are taking BARACLUDE Oral Solution, carefully measure your dose with the spoon provided, as follows:

  1. 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.

  2. Swallow the medicine directly from the measuring spoon.

  3. 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. Your hepatitis B symptoms may get worse or become very serious if you stop taking BARACLUDE.** After you stop taking BARACLUDE, it is

important to stay under your healthcare provider's care. Your healthcare provider will need to do regular blood tests to check your liver.

- **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, get more from your healthcare provider or pharmacy. **Do not run out of BARACLUDE** (entecavir).
- **If you take more than the prescribed dose of BARACLUDE,** call your healthcare provider right away.

What are the possible side effects of BARACLUDE?

BARACLUDE may cause the following serious side effects (see "**What is the most important information I should know about BARACLUDE?**"):

- **a worse or very serious hepatitis if you stop taking it.**
- **lactic acidosis and liver problems.**

The most common side effects of BARACLUDE are headache, tiredness, dizziness, and nausea. Less common side effects include diarrhea, indigestion, vomiting, sleepiness, and trouble sleeping. There have also been occasional reports of rash and hair loss. In some patients, the results of blood tests that measure how the liver or pancreas is working may worsen.

These are not all the side effects of BARACLUDE. The list of side effects is **not** complete at this time because BARACLUDE is still under study. Report any new or continuing symptom to your healthcare provider. If you have questions about side effects, ask your healthcare provider. Your healthcare provider may be able to help you manage these side effects.

How should I store BARACLUDE?

- Store BARACLUDE Tablets or Oral Solution at room temperature, 59° to 86° F (15° to 30° C). They do not require refrigeration. Do not store BARACLUDE Tablets in a damp place such as a bathroom medicine cabinet or near the kitchen sink.
- Keep the container tightly closed. BARACLUDE Oral Solution should be stored in the original carton and protected from light.
- **Keep BARACLUDE and all medicines out of the reach of children and pets at all times.** Do not keep medicine that is out of date or that you no longer need. Dispose of unused medicines through community take-back disposal programs when available or place BARACLUDE in an unrecognizable closed container in the household trash.

General information about BARACLUDE: Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. 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. The 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. You can also call 1-800-321-1335 or visit the BARACLUDE website at *www.Baraclude.com*.

What are the ingredients in BARACLUDE?

Active Ingredient: entecavir

Inactive Ingredients in BARACLUDE Tablets: lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, magnesium stearate, 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.

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

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