Baraclude® (Entecavir)

DESCRIPTION

BARACLUDE® (entecavir) is a guanosine nucleoside analogue with potent and selective activity against hepatitis B virus (HBV).

BARACLUDE® is available for oral administration as film-coated tablets in strength of 0.5 mg of entecavir.

INDICATIONS

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 patients with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease (see **CLINICAL TRIAL INFORMATION**).
- Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease (see **UNDESIRABLE EFFECTS** and **CLINICAL TRIAL INFORMATION**).
- Virologic, biochemical, serologic, and safety data are available for a limited number of adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy (see **WARNINGS AND PRECAUTIONS FOR USE** and **CLINICAL TRIAL INFORMATION**).

DOSAGE AND ADMINISTRATION

Recommended dosage

Compensated liver disease

Nucleoside-naïve patients: The recommended dose of BARACLUDE® is 0.5 mg orally once daily with or without food.

Lamivudine-refractory patients (i.e., history of hepatitis B viremia while receiving lamivudine therapy or known lamivudine resistance [LVDr, commonly called YMDD] mutations): The recommended dose is 1 mg once daily. BARACLUDE® should be taken orally, on an empty stomach (empty means at least 2 hours before and at least 2 hours after a meal).

Decompensated liver disease

The recommended dose for patients with decompensated liver disease is 1 mg once daily, which must be taken on an empty stomach (empty means at least 2 hours before and at least 2 hours after a meal).

Special Populations

Patients with renal impairment

Entecavir is predominantly eliminated by the kidney (see **PHARMACOLOGICAL PROPERTIES: Pharmacokinetics:** *Metabolism and elimination*). The clearance of entecavir decreases with impaired (decreasing) creatinine clearance (see **PHARMACOLOGICAL PROPERTIES: Pharmacokinetics: Special Populations:** *Patients with renal impairment*). Dosage adjustment of BARACLUDE® is recommended for patients who have a creatinine clearance <50 mL/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in Table 1 .

Table 1: Recommended Dosage of BARACLUDE® in Patients with Renal Impairment[a]:

Creatinine Clearance (mL/min)	**Usual Dose (0.5 mg once daily)**	**Lamivudine-Refractory or Decompensated Liver Disease (1 mg once daily)**
30 – <50	0.5 mg every 48 hours	0.5 mg once daily OR 1 mg every 48 hours
10 – <30	0.5 mg every 72 hours	1 mg every 72 hours
<10	0.5 mg every 5–7 days	1 mg every 5–7 days

Hemodialysis[b] or CAPD	0.5 mg every 5–7 days	1 mg every 5–7 days

[a] Do not split tablets.

[b] On hemodialysis days, administer BARACLUDE® after hemodialysis.

CAPD=continuous ambulatory peritoneal dialysis.

Patients with hepatic impairment

No dosage adjustment of BARACLUDE® is required in patients with hepatic impairment.

Pediatric and adolescent patients

The safety and efficacy of BARACLUDE® in patients <16 years of age have not been established.

Geriatric patients

No dosage adjustment of BARACLUDE® based on age is required.

CONTRAINDICATIONS

BARACLUDE® is contraindicated in patients with previously demonstrated hypersensitivity to entecavir or any component of the product.

WARNINGS AND PRECAUTIONS FOR USE

Drug-class-specific Warnings and Precautions

Lactic acidosis/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.

Exacerbations of hepatitis after discontinuation of treatment

Acute exacerbation of hepatitis has been reported in patients who have discontinued HBV therapy, including therapy with BARACLUDE® (see **UNDESIRABLE EFFECTS: Exacerbations of hepatitis after discontinuation of treatment**).

The majority of post-treatment exacerbations appear to be self-limited. However, severe exacerbations, including fatalities, may occur. The causal relationship of these events to discontinuation of therapy is unknown. Hepatic function should be monitored at repeated

intervals after discontinuation of therapy. If appropriate, resumption of HBV therapy may be warranted.

Product-specific Warnings and Precautions

Co-infection with HIV

BARACLUDE® has not been evaluated in patients who are co-infected with human immunodeficiency virus (HIV) and HBV and are not concurrently receiving effective HIV treatment. Limited clinical experience suggests there is a potential for the development of HIV resistance if BARACLUDE® is used to treat chronic hepatitis B infection in patients with untreated HIV infection (see **PHARMACOLOGICAL PROPERTIES: Antiviral activity**). Therefore, therapy with BARACLUDE® is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART). See **UNDESIRABLE EFFECTS: Patients Co-infected with HIV** and **CLINICAL TRIAL INFORMATION: Patients Co-infected with HIV and HBV** for efficacy and safety data for BARACLUDE® from a study of HIV/HBV co-infected patients receiving a lamivudine-based HAART regimen. BARACLUDE® has not been studied as a treatment for HIV infection and is not recommended for this use.

Patients with renal impairment

Dosage adjustment of BARACLUDE® is recommended for patients with renal impairment (see **DOSAGE AND ADMINISTRATION:** *Patients with renal impairment*).

Liver transplant recipients

Limited data are available on the safety and efficacy of BARACLUDE® in liver transplant recipients. In a single-arm, open-label study, patients who had HBV DNA less than 172 IU/mL at the time of transplant were treated with BARACLUDE® 1 mg once daily post-transplant. The frequency and nature of adverse events in this study were consistent with those expected in patients who have received a liver transplant and the known safety profile of BARACLUDE®. None of the 61 evaluable patients had virologic recurrence. (See **CLINICAL TRIAL INFORMATION: Liver transplant recipients**.) Renal function should be carefully monitored before and during BARACLUDE® therapy in liver transplant recipients receiving an immunosuppressant that may affect renal function, such

as cyclosporine or tacrolimus (see **DOSAGE AND ADMINISTRATION:** *Patients with hepatic impairment,* **PHARMACOLOGICAL PROPERTIES: Pharmacokinetics: Special Populations:** *Patients with hepatic impairment,* and *Liver transplant recipients*).

Patients with decompensated liver disease

A higher rate of serious hepatic adverse events (regardless of causality) has been observed in patients with decompensated liver disease, in particular in those with Child-Turcotte-Pugh (CTP) class C disease, compared with rates in patients with compensated liver function. Also, patients with decompensated liver disease may be at higher risk for lactic acidosis and for specific renal adverse events such as hepatorenal syndrome. Therefore, clinical and laboratory parameters should be closely monitored in this patient population (see also **UNDESIRABLE EFFECTS** and **CLINICAL TRIAL INFORMATION:** *Patients with decompensated liver disease*).

Patient information

Patients should be advised that therapy with BARACLUDE® has not been proven to reduce the risk of transmission of HBV and, therefore, appropriate precautions should still be taken.

Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women. BARACLUDE® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are no data on the effect of entecavir on transmission of HBV from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV.

Entecavir is excreted in the milk of rats. It is not known whether it is excreted in human milk. Mothers should be instructed not to breast-feed if they are taking BARACLUDE®.

Pediatric Use

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

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Medicinal Products

Since entecavir is predominantly eliminated by the kidney **(**see **PHARMACOLOGICAL PROPERTIES: Pharmacokinetics:** *Metabolism and elimination***)**, coadministration of BARACLUDE® with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of either medicinal product. Coadministration of BARACLUDE® with either lamivudine, adefovir dipivoxil or tenofovir disoproxil fumarate resulted in no significant drug interactions. The effects of coadministration of BARACLUDE® with other medicinal products that are excreted renally or affect renal function have not been evaluated. Patients should be monitored closely for adverse events when BARACLUDE® is coadministered with such medicinal products.

Food

Administration of entecavir with food decreased absorption by 18-20% (see **DOSAGE AND ADMINISTRATION** and **PHARMACOLOGICAL PROPERTIES: Pharmacokinetics:** *Absorption*).

UNDESIRABLE EFFECTS

Assessment of adverse reactions is based on four clinical studies in which 1720 patients with chronic HBV 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 107 weeks. The safety profiles of BARACLUDE® and lamivudine were comparable in these studies. Among BARACLUDE®-treated patients, the most common adverse events of any severity with at least a possible relation to BARACLUDE® were headache (9%), fatigue (6%), dizziness (4%), and nausea (3%).

In these clinical studies, the 594 BARACLUDE®-treated patients who received blinded therapy for more than 52 weeks reported adverse reactions similar in nature and severity to those reported during the first 52 weeks of treatment.

Clinical Events

Nucleoside naïve patients

In two double-blind, lamivudine-controlled studies, one with patients who tested positive for the hepatitis B e antigen (HBeAg) and one with HBeAg-negative patients, 679 nucleoside naïve patients received BARACLUDE® 0.5 mg once daily for a median of 54 weeks. Adverse reactions of moderate intensity or greater and considered at least possibly related to treatment with BARACLUDE® are listed by body system organ class. Frequency is defined as very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100).

Psychiatric disorders:	uncommon: insomnia
Nervous system disorders:	common: headache
	uncommon: dizziness, somnolence
Gastrointestinal disorders:	uncommon: nausea, diarrhea, dyspepsia, vomiting
General disorders and administration site conditions:	common: fatigue

Lamivudine-refractory Patients

In two double-blind, lamivudine-controlled studies, 183 lamivudine-refractory patients received BARACLUDE® 1 mg once daily for a median of 69 weeks. Adverse reactions of moderate intensity or greater and considered at least possibly related to treatment with BARACLUDE® are listed by body system organ class. Frequency is defined as very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100).

Nervous system disorders:	common: headache
Gastrointestinal disorders:	common: diarrhea, dyspepsia
General disorders and	common: fatigue

administration site conditions:

Laboratory Findings

Table 2 shows laboratory findings from four double-blind, lamivudine-controlled clinical studies in which 679 nucleoside- naïve patients received BARACLUDE® 0.5 mg once daily for a median of 54 weeks and 183 lamivudine-refractory patients received BARACLUDE® 1 mg for a median of 69 weeks.

Table 2: Selected Laboratory Abnormalities Reported During Treatment in Four Clinical Trials

Test	Nucleoside Naïve[a] BARACLUDE® 0.5 mg n=679	Lamivudine-Refractory[b] BARACLUDE® 1 mg n=183
ALT >10 × ULN and >2 × baseline	2%	2%
ALT >3 × baseline	5%	4%
ALT >2 × baseline and **total bilirubin** >2 × ULN and >2 × baseline	<1%	<1%
Albumin <2.5 g/dL	<1%	0
Amylase >3 × baseline	2%	2%
Lipase >3 × baseline	12%	18%
Platelets <50,000/mm^3	<1%	<1%

[a] Median duration of therapy was 54 weeks.

[b] Median duration of therapy was 69 weeks.

ULN=upper limit of normal.

Among BARACLUDE®-treated patients in these studies, on-treatment ALT elevations >10 × ULN and >2 × 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

Acute exacerbations of hepatitis have been reported in patients who have discontinued anti-HBV therapy, including therapy with BARACLUDE® (see **WARNINGS AND PRECAUTIONS FOR USE: Drug-class-specific Warnings and Precautions**). The frequency of exacerbation of hepatitis or ALT flare (defined as ALT >10 × ULN and 2 × the patient's reference level) during off-treatment follow-up in clinical studies with BARACLUDE® is presented in Table 3.

Table 3: Exacerbations of Hepatitis During Off-Treatment Follow-up in Three Clinical Trials

	Patients with ALT Elevations >10 × ULN and >2 × Reference[a]	
	BARACLUDE®	**Lamivudine**
Nucleoside naïve	28/476 (6%)	43/417 (10%)
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 patients and 10 weeks for lamivudine-treated patients.

Decompensated liver disease

Additional adverse reactions observed in BARACLUDE®-treated patients in a study in which BARACLUDE® 1 mg/day was compared with adefovir dipivoxil in patients with chronic hepatitis B infection and decompensated liver disease include decrease in blood bicarbonate (2%) and renal failure (<1%). The on-study cumulative death rate was 23% (23/102), and causes of death were generally liver-related, as expected in this population. The on-study cumulative rate of hepatocellular carcinoma (HCC) was 12% (12/102).

Laboratory test abnormalities: Through 48 weeks among BARACLUDE®-treated patients, none had ALT elevations both >10 times ULN and >2 times baseline, and 1% of patients had ALT elevations >2 times baseline together with total bilirubin >2 times ULN and >2 times baseline. Albumin levels <2.5 g/dL occurred in 30% of patients, lipase levels >3 times baseline in 10%, and platelets <50,000/mm^3 in 20%.

Patients Co-infected with HIV

Patients co-infected with HBV and HIV who experienced recurrence of HBV viremia while receiving a lamivudine-containing highly active antiretroviral regimen were treated with their lamivudine-containing regimen (lamivudine dose, 300 mg/day) and either BARACLUDE® 1 mg once daily (n=51) or placebo (n=17). After 24 weeks of double-blind therapy and a mean of 17 weeks of open-label therapy (where all patients received BARACLUDE®), the adverse event and laboratory abnormality profiles were similar for the BARACLUDE® and placebo treatment groups. BARACLUDE® has not been evaluated in HIV/HBV co-infected patients who are not concurrently receiving effective IV treatment (see **WARNINGS AND PRECAUTIONS FOR USE: Product-specific Warnings and Precautions:** *Co-infection with HIV*).

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 4.

Table 4: Principal Analyses of Time to Adjudicated Events - Randomized Treated Subjects

Endpoint[c]	Number of Subjects with Events		
	BARACLUDE N=6,216	Non-ETV N=6,162	Hazard Ratio [BARACLUDE:Non-ETV] (CI[a])
Primary Endpoints			
Overall malignant neoplasm	331	337	0.93 (0.800, 1.084)
Liver-related HBV disease progression	350	375	0.89 (0.769, 1.030)
Death	238	264	0.85 (0.713, 1.012)
Secondary Endpoints			
Non-HCC malignant neoplasm	95	81	1.10 (0.817, 1.478)
HCC	240[b]	263	0.87 (0.727, 1.032)

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. Liver-related HBV disease progression is a composite event of liver-related death, HCC, or non-HCC HBV disease progression.

CI = confidence interval; N = total number of subjects.

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 events have been identified during post-approval use of BARACLUDE®. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Immune system disorders: Anaphylactoid reaction.
Metabolism and nutrition disorders: Lactic acidosis has been reported, often in association with hepatic decompensation, other serious medical conditions, or drug exposures. Patients with decompensated cirrhosis may be at higher risk for lactic acidosis.
Hepatobiliary disorders: Increased transaminases.
Skin and subcutaneous tissue disorders: Alopecia, rash.

OVERDOSAGE

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Mechanism of action

Entecavir is a guanosine nucleoside analogue with potent and selective activity against HBV polymerase. It is phosphorylated to the active triphosphate (TP) form, which has an intracellular half-life of 15 hours. Intracellular TP levels are directly related to extracellular entecavir concentrations, with no significant accumulation beyond initial plateau levels. By competing with the natural substrate deoxyguanosine-TP, entecavir-TP inhibits all 3 functional activities of the viral polymerase: (1) priming of the HBV polymerase, (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand HBV DNA. The entecavir-TP K_i for HBV DNA polymerase is 1.2 nM. Entecavir-TP is a weak inhibitor of cellular DNA polymerases α, β, and δ with K_i values of 18 to 40 μM. In addition, high exposures of entecavir-TP and entecavir had no

relevant adverse effects on γ polymerase (K_i >160 μM) or mitochondrial DNA synthesis in HepG2 cells.

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 (rtM204V, rtL180M) was 0.026 μM (range 0.010-0.059 μM).

A comprehensive analysis of the inhibitory activity of entecavir against a panel of laboratory and clinical HIV-1 isolates using a variety of cells and assay conditions yielded EC_{50}s ranging from 0.026 to >10 μM. Inhibitory activity at concentrations ~1 μM was only observed when cell culture assay conditions were modified in a way that decreased the level of virus used to initiate infection. In cell culture, entecavir selected for an M184I substitution 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

Compared to activity against wild-type HBV, there is an 8-fold reduction in susceptibility to entecavir in cell-based studies when lamivudine and telbivudine resistance-associated substitutions rtM204I/V ± rtL180M (LVDr) are present. At extracellular concentrations representative of plasma levels achieved with 1-mg dosing, intracellular entecavir-TP levels would be expected to surpass those needed to inhibit the enzyme activity of lamivudine-resistant HBV polymerases. Recombinant viruses encoding adefovir-resistant substitutions at either rtN236T or rtA181V remained fully susceptible to entecavir.

Clinical resistance

Patients in clinical trials initially treated with entecavir 0.5 mg (nucleoside-naïve) or 1.0 mg (lamivudine-refractory) and with an on-therapy PCR HBV DNA measurement at or after Week 24 were monitored for resistance. Virologic breakthroughs due to resistance to

entecavir require the existence of primary LVDr substitutions (M204I/V ± L180M) along with an additional substitution at residues T184, S202, or M250 of the polymerase protein.

Nucleoside-naïve studies: Through 240 weeks in nucleoside-naïve studies genotypic evidence of entecavir resistance (ETVr) substitutions at rtT184, rtS202, or rtM250 was observed in 3 patients treated with entecavir, 2 of whom experienced virologic breakthrough, as shown in Table 5.

Table 5: Genotypic Entecavir Resistance Through Year 5, Nucleoside-Naïve Studies

	Year 1	**Year 2**	**Year 3[a]**	**Year 4[a]**	**Year 5[a]**
Patients treated and monitored for resistance[b]	663	278	149	121	108
Patients in specific year with:					
emerging genotypic ETVr[c, d]	1	1	1	0	0
genotypic ETVr[c, d] with virologic breakthrough[e]	1	0	1	0	0%
Cumulative probability of:					
emerging genotypic ETVr[c, d]	0.2%	0.5%	1.2%	1.2%	1.2%
genotypic ETVr[c, d] with virologic breakthrough[e]	0.2%	0.2%	0.8%	0.8%	0.8%

[a] Results reflect use of a 1-mg dose of entecavir for 147 patients in Year 3 and all patients in Years 4 and 5 of combination entecavir-lamivudine therapy (followed by long-term entecavir therapy) for a median of 20 weeks for 130 patients in Year 3 and for 1 week for 1 patient in Year 4 in a rollover study.

[b] Includes patients with at least one on-therapy HBV DNA measurement by PCR at or after Week 24 through Week 58 (Year 1), after Week 58 through Week 102 (Year 2), after Week 102 through Week 156 (Year 3), after Week 156 through Week 204 (Year 4), or after Week 204 through Week 252 (Year 5).

[c] ETVr = entecavir resistance substitutions at residues rtT184, rtS202, or rtM250.

[d] Patients also had lamivudine resistance substitutions (rtM204V and rtL180M).

[e] >1 $\log_{10}$ increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point.

Lamivudine-refractory studies: Genotypic analysis of clinical samples from lamivudine-refractory patients identified emerging ETVr substitutions in 11 of 187 patients in Year 1, 12 of 146 patients in Year 2, 16 of 80 patients in Year 3, 6 of 52 patients in Year 4, and 2 of 33 patients in Year 5 as shown in Table 6.

Table 6: Genotypic Entecavir Resistance Through Year 5, Lamivudine-Refractory Studies

	Year 1	Year 2	Year 3[a]	Year 4[a]	Year 5[a]
Patients treated and monitored for resistance[b]	187	146	80	52	33
Patients in specific year with: emerging genotypic ETVr[c,d]	11	12	16	6	2
genotypic ETVr[c, d] with virologic breakthrough	2[f]	14[f]	13[f]	9[f]	1[f]
Cumulative probability of: emerging genotypic ETVr[c,d]	6%	15%	36%	47%	51%
genotypic ETVr[c, d] with virologic breakthrough[e]	1%[f]	11%[f]	27%[f]	41%[f]	44%[f]

[a] Results reflect use of combination entecavir-lamivudine therapy (followed by long-term entecavir therapy) for a median of 13 weeks for 48 patients in Year 3, a median of 38 weeks for 10 patients in Year 4, and for 16 weeks for 1 patient in Year 5 in a rollover study.

[b] Includes patients with at least one on-therapy HBV DNA measurement by PCR at or after Week 24 through Week 58 (Year 1), after Week 58 through Week 102 (Year 2), or after Week 102 through Week 156 (Year 3), after Week 156 through Week 204 (Year 4), or after Week 204 through Week 252 (Year 5).

[c] ETVr = entecavir resistance substitutions at residues rtT184, rtS202, or rtM250.

[d] Patients also had lamivudine resistance substitutions (rtM204V/I ± rtL180M).

[e] >1 $\log_{10}$ increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point.

[f] ETVr occurring in any year, virologic breakthrough in specified year.

The presence of ETVr substitutions at baseline in isolates from 10 (5%) of 187 lamivudine-refractory patients indicates that prior lamivudine treatment can select these resistance substitutions and that they can exist at a low frequency before entecavir treatment. Through Week 240, 3 of these 10 patients experienced virologic breakthrough.

Pharmacokinetics

Absorption

In healthy subjects, entecavir was rapidly absorbed with peak plasma concentrations occurring between 0.5 and 1.5 hours. There was a dose-proportionate increase in peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) values following multiple doses ranging from 0.1 to 1 mg. Steady-state was achieved after 6-10 days of once-daily dosing with approximately 2-fold accumulation. C_{max} and trough plasma concentration (C_{trough}) at steady-state were 4.2 and 0.3 ng/mL, respectively, for a 0.5-mg dose, and 8.2 and 0.5 ng/mL, respectively, for a 1-mg dose.

Oral administration of entecavir 0.5 mg 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 minimal delay in absorption (1.0-1.5 hours fed vs. 0.75 hour fasted), a decrease in C_{max} of 44-46%, and a decrease in AUC of 18-20%. (See **DOSAGE AND ADMINISTRATION**.)

Distribution

The estimated volume of distribution for entecavir was in excess of total body water, suggesting that it has good penetration into tissues. Protein binding to human serum protein *in vitro* was approximately 13%.

Metabolism and elimination

Entecavir is not a substrate, inhibitor, or inducer of the CYP450 enzyme system. At concentrations 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 approximately 340-fold higher than those observed in humans, entecavir did not induce the human CYP450 enzymes 1A2, 2C9, 2C19, 3A4, 3A5, and 2B6. Following administration of ^{14}C-entecavir in humans and rats, no oxidative or

acetylated metabolites and minor amounts of phase II metabolites (glucuronide and sulfate conjugates) were observed.

After reaching peak levels, 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 about 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 dose. Renal clearance is independent of dose and ranges between 360 and 471 mL/min suggesting that entecavir undergoes both glomerular filtration and net tubular secretion.

Special Populations

Patients with renal impairment

Based on the results of a study of the pharmacokinetics of a single 1-mg dose of entecavir in patients with renal impairment (Table 7), dosage adjustment is recommended for patients who have a creatinine clearance <50 mL/min. (See **DOSAGE AND ADMINISTRATION:** *Patients with renal impairment.*)

Table 7: Pharmacokinetic Parameters of Entecavir in Subjects with Selected Degrees of Renal Impairment

	Renal Function Group					
	Baseline Creatinine Clearance (mL/min)				**Severe Managed with Hemodialysis (n=6)**	**Severe Managed with CAPD (n=4)**
	Unimpaired >80 (n=6)	**Mild >50 -≤80 (n=6)**	**Moderate 30-50 (n=6)**	**Severe <30 (n=6)**		
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•hr/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)

CLR=renal clearance; CLT/F=apparent oral clearance; CAPD=continuous ambulatory peritoneal dialysis.

A 4-hour period of hemodialysis removed approximately 13% of the dose, and 0.3% was removed by CAPD.

Patients with hepatic impairment

Pharmacokinetic parameters of entecavir in patients with hepatic impairment were similar to those in patients with normal hepatic function.

Geriatric

The pharmacokinetic profile of entecavir does not differ by age.

Gender/Race

The pharmacokinetic profile of entecavir does not differ by gender or race.

Liver transplant recipients

Entecavir exposure in HBV-infected liver transplant recipients on a stable dose of cyclosporine A (n=5) or tacrolimus (n=4) 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 patients (see **WARNINGS AND PRECAUTIONS FOR USE: Product-specific Warnings and Precautions:** *Liver transplant recipients*).

CLINICAL TRIAL INFORMATION

The demonstration of benefit of BARACLUDE® is based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment naïve and lamivudine-resistant adult patients with HBeAg-positive or HBeAg-negative chronic HBV infection and compensated liver disease. Efficacy and safety were evaluated in three active-controlled clinical trials including 1633 patients with chronic HBV infection (serum

HBsAg-positive for at least 6 months) accompanied by evidence of viral replication (detectable serum HBV DNA). Patients had persistently elevated ALT levels ≥1.3 times ULN and chronic inflammation on liver biopsy compatible with a diagnosis of chronic viral hepatitis.

According to protocol-mandated criteria, patients in these three clinical trials discontinued treatment with study drug after 52 weeks according to a definition of response based on HBV virologic suppression (<0.7 Meg/mL by bDNA assay) and loss of HBeAg (in HBeAg-positive patients) or ALT <1.25 × ULN (in HBeAg-negative patients) at Week 48. Patients who achieved virologic suppression but did not have serologic response (HBeAg-positive) or did not achieve ALT <1.25 × ULN (HBeAg-negative) continued blinded dosing through 96 weeks or until the response criteria were met. These protocol-specified patient management guidelines are not intended as guidance for clinical practice.

BARACLUDE® has also been studied in adult patients with HIV/HBV co-infection who have received prior lamivudine therapy.

Nucleoside naïve patients with compensated liver disease

Outcomes at 48 weeks

Results at 48 weeks for two randomized, double-blind studies in nucleoside naïve patients, one in HBeAg-positive and the other in HBeAg-negative patients, comparing entecavir to lamivudine are presented in Table 8.

Table 8: Histologic, Virologic, Biochemical, and Serologic Endpoints at Week 48, Nucleoside-Naïve Patients

	HBeAg-Positive		HBeAg-Negative	
	ETV 0.5 mg once daily	**LVD 100 mg once daily**	**ETV 0.5 mg once daily**	**LVD 100 mg once daily**
N	314[a]	314[a]	296[a]	287[a]
Histologic improvement[b]	72%*	62%	70%*	61%
Ishak fibrosis score improvement	39%	35%	36%	38%
Ishak fibrosis score worsening	8%	10%	12%	15%

N	354	355	325	313
Viral load reduction (log_{10} copies/mL)[c]	-6.86*	-5.39	-5.04*	-4.53
HBV DNA undetectable (<300 copies/mL)[c]	67%*	36%	90%*	72%
ALT normalization (≤1 × ULN)	68%*	60%	78%*	71%
HBeAg seroconversion	21%	18%		

*p value vs. lamivudine ≤0.05.

[a] patients with evaluable baseline histology (baseline Knodell Necroinflammatory Score ≥2).

[b] a primary endpoint defined as a ≥2-point decrease in Knodell necroinflammatory score from baseline with no worsening of the Knodell fibrosis score.

[c] Roche Cobas Amplicor PCR assay (LLOQ = 300 copies/mL).

Outcomes beyond 48 weeks

HBeAG-positive

At end of dosing, among HBeAg-positive patients who continued treatment beyond 52 weeks (median of 96 weeks), 74% of 243 BARACLUDE®-treated and 37% of 164 lamivudine-treated patients had HBV DNA <300 copies/mL by PCR while ALT normalization (≤1 times ULN) occurred in 79% BARACLUDE®-treated and 68% of lamivudine-treated patients.

Through 96 weeks, cumulative confirmed outcomes for HBeAg-positive patients (all treated) demonstrate that continued treatment with BARACLUDE® (n=354) resulted in an increase in the proportion of patients with HBV DNA <300 copies/mL by PCR (80%) and ALT normalization (87%). Through the last observation on or off treatment, 31% of BARACLUDE®-treated patients had HBeAg seroconversion and 5% had HBsAg loss. In the lamivudine treatment group (n=355), cumulative confirmed HBV DNA <300 copies/mL by PCR occurred in 39% of patients and ALT normalization in 79%; 26% of patients had HBeAg seroconversion and 3% had HBsAg loss. The difference between treatment groups was statistically significant for percentage of patients with HBV DNA <300 copies/mL and ALT normalization ($p<0.01$).

HBeAg-negative

For 26 BARACLUDE®-treated and 28 lamivudine-treated HBeAg-negative patients who continued treatment beyond 52 weeks (median 96 weeks), 85% of BARACLUDE®-treated and 57% of lamivudine-treated patients had HBV DNA <300 copies/mL by PCR at end of dosing. ALT normalization (≤1 times ULN) occurred in 27% of BARACLUDE®-treated and 21% of lamivudine-treated patients at end of dosing.

Through 96 weeks for HBeAg-negative patients, 94% of BARACLUDE®-treated patients (n=325) and 77% of lamivudine-treated patients (n=313) had cumulative confirmed HBV DNA <300 copies/mL ($p<0.01$). ALT normalization occurred in 89% of BARACLUDE®-treated patients and 84% of lamivudine-treated patients.

Liver biopsy results

Of the 679 BARACLUDE®-treated patients in the two nucleoside-naïve studies, 293 (43%) eligible patients enrolled in a long-term rollover study and continued BARACLUDE® therapy. Patients in the rollover study received BARACLUDE® 1 mg once daily. Sixty-nine of the 293 patients elected to have a repeat liver biopsy after a total treatment duration of more than 144 weeks (3 years). Fifty-seven patients had both an evaluable baseline and long-term biopsy, with a median duration of BARACLUDE® therapy of 280 weeks (approximately 6 years). Ninety-six percent of these patients had Histologic Improvement as previously defined (see Table 8, footnote b), and 88% had a >1-point decrease in Ishak fibrosis score. Of the 43 patients with a baseline Ishak fibrosis score of >2, 58% had a >2-point decrease. At the time of the long-term biopsy, 57 (100%) of patients had HBV DNA <300 copies/mL and 49 (86%) had serum ALT <1 × ULN.

Experience in lamivudine-refractory patients

Outcomes at 48 weeks

Results at 48 weeks for a randomized, double-blind study comparing entecavir to lamivudine in HBeAg-positive lamivudine-refractory patients, with 85% of patients presenting LVDr mutations at baseline, are presented in Table 9.

Table 9: Histologic, Virologic, Biochemical, and Serologic Endpoints at Week 48, Lamivudine-Refractory Patients

	ETV 1.0 mg once daily	LVD 100 mg once daily
N	124[a]	116[a]
Histologic improvement[b]	55%*	28%
Ishak fibrosis score improvement	34%*	16%
Ishak fibrosis score worsening	11%	26%
N	141	145
Viral load reduction (log_{10} copies/mL)[c]	-5.11*	-0.48
HBV DNA undetectable (<300 copies/mL)[c]	19%*	1%
ALT normalization (≤1 times ULN)	61%*	15%
HBeAg seroconversion	8%	3%

*p value vs. lamivudine ≤0.01.

[a] patients with evaluable baseline histology (baseline Knodell Necroinflammatory Score ≥2).

[b] a primary endpoint defined as a ≥2-point decrease in Knodell Necroinflammatory score from baseline with no worsening of the Knodell fibrosis score.

[c] Roche Cobas Amplicor PCR assay (LLOQ = 300 copies/mL).

Outcomes beyond 48 weeks

For the 77 lamivudine-refractory patients who continued BARACLUDE® treatment beyond 52 weeks (median 96 weeks), 40% of patients had HBV DNA <300 copies/mL by PCR and 81% had ALT normalization (≤1 times ULN) at end of dosing.

Cumulative confirmed outcomes through 96 weeks for all treated lamivudine-refractory patients (n=141) demonstrate that continued treatment with BARACLUDE® resulted in an increase in the proportion of patients with HBV DNA <300 copies/mL by PCR (30%) and ALT normalization (85%). Through the last observation on or off treatment, 17% of BARACLUDE®-treated patients had HBeAg seroconversion. The difference between the BARACLUDE® and lamivudine treatment groups was statistically significant on all three parameters ($p<0.01$).

Post-Treatment Follow-up

For the 31% of nucleoside naïve, HBeAg-positive BARACLUDE®-treated patients who met response criteria (virologic suppression by bDNA assay and loss of HBeAg) and discontinued therapy, response was sustained in 75% throughout the 24-week post-treatment follow-up period. For the 88% of nucleoside naïve, HBeAg-negative BARACLUDE®-treated patients who met response criteria (virologic suppression by bDNA assay and ALT <1.25 × ULN), response was sustained in 46% throughout the 24-week post-treatment follow-up period. Of the 22 (16%) lamivudine-refractory patients who met response criteria (virologic response on bDNA assay and loss of HBeAg) while receiving BARACLUDE®, response was sustained in 11 (50%) throughout the 24-week post-treatment follow-up period.

Patients with decompensated liver disease

In a randomized open-label study, 191 patients 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, received BARACLUDE® 1 mg once daily or adefovir dipivoxil 10 mg once daily. Patients were either HBV-treatment-naïve or pretreated (excluding pretreatment with BARACLUDE®, adefovir dipivoxil, or tenofovir disoproxil fumarate). BARACLUDE® was superior to adefovir dipivoxil on the primary efficacy endpoint of mean change from baseline in serum HBV DNA by PCR at 24 weeks. Results for selected study endpoints at 24 and 48 weeks are shown in Table 10.

Table 10: Selected Endpoints at Weeks 24 and 48, Patients with Decompensated Liver Disease

	Week 24		Week 48	
	ETV 1 mg (n=100)	ADV 10 mg (n=91)	ETV 1 mg (n=100)	ADV 10 mg (n=91)
HBV DNA[a]				
Proportion undetectable (<300 copies/mL)	49%*	16%	57%*	20%

Mean change from baseline (log_{10} copies/mL)	−4.48*	−3.40	−4.66	−3.90
Stable or improved CTP score[b]	66%	71%	61%	67%
Model for End-Stage Liver Disease (MELD) score Mean change from baseline[c]	−2.0	−0.9	−2.6	−1.7
HBsAg loss	1%	0	5%	0
Normalisation of:[d]				
ALT (≤1 × ULN)	46/78 (59%)*	28/71 (39%)	49/78 (63%)*	33/71 (46%)
Albumin (≥1 × LLN)	20/82 (24%)	14/69 (20%)	32/82 (39%)	20/69 (29%)
Bilirubin (≤1 × ULN)	12/75 (16%)	10/65 (15%)	15/75 (20%)	18/65 (28%)
Prothrombin time (≤1 × ULN)	9/95 (9%)	6/82 (7%)	8/95 (8%)	7/82 (9%)

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

[b] Defined as decrease or no change from baseline in CTP score.

[c] Baseline mean MELD score was 17.1 for ETV and 15.3 for adefovir dipivoxil.

[d] Denominator is patients with abnormal values at baseline.

* $p<0.05$

ETV+entecavir, ADV+adefovir dipivoxil, ULN = upper limit of normal, LLN = lower limit of normal

The time to onset of HCC or death (whichever occurred first) was comparable in the two treatment groups.

Patients Co-infected with HIV and HBV

A randomized, double-blind, placebo-controlled study compared BARACLUDE® with placebo in 68 patients co-infected with HIV/HBV who presented with recurrence of HBV viremia on a lamivudine-containing HAART regimen. Patients continued their lamivudine-regimen and were assigned to add either BARACLUDE® 1 mg once daily (n=51) or

placebo (n=17) for 24 weeks followed by an open-label phase for an additional 24 weeks where all received BARACLUDE®. At 24 weeks, a reduction in HBV viral load by PCR was observed with BARACLUDE® (−3.65 $\log_{10}$ copies/mL), whereas a slight increase was measured with placebo (+0.11 $\log_{10}$ copies/mL, $p<0.0001$). Six percent of BARACLUDE®-treated patients and no placebo-treated patients had HBV DNA by PCR <300 copies/mL, while 34% of BARACLUDE®-treated and 8% of placebo-treated patients with abnormal ALT at baseline had ALT normalization (≤1 × ULN). At the end of the open-label phase (Week 48), the mean change from baseline HBV DNA by PCR for patients originally assigned to BARACLUDE® was −4.20 $\log_{10}$ copies/mL; 8% of patients had HBV DNA <300 copies/mL by PCR; and 37% of patients with abnormal ALT at baseline had ALT normalization. BARACLUDE® has not been evaluated in HIV/HBV co-infected patients who are not concurrently receiving effective HIV treatment (see **WARNINGS AND PRECAUTIONS FOR USE: Product-specific Warnings and Precautions:** *Co-infection with HIV*).

Liver transplant recipients

The safety and efficacy of BARACLUDE®1 mg once daily were assessed in a single-arm, open-label study in 65 patients who received a liver transplant for complications of chronic HBV infection and had HBV DNA <172 IU/mL (approximately 1000 copies/mL) at the time of transplant. The study population was 82% male, 39% Caucasian, and 37% Asian, with a mean age of 49 years; 89% of patients had HBeAg-negative disease at the time of transplant. Of the 61 patients who were evaluable for efficacy (received BARACLUDE® for at least 1 month), 60 also received hepatitis B immune globulin as part of the post-transplant prophylaxis regimen. At Week 72 post-transplant, none of the evaluable patients had HBV recurrence [defined as HBV DNA ≥50 IU/mL (approximately 300 copies/mL)] by last-observation-carried forward analysis. The frequency and nature of adverse events in this study were consistent with those expected in patients who have received a liver transplant and the known safety profile of BARACLUDE®.

NON-CLINICAL SAFETY

Carcinogenicity, Mutagenesis, and Impairment of Fertility

Two-year carcinogenicity studies with entecavir were conducted in mice and rats. In male mice, increases in the incidences of lung tumors were observed at entecavir exposures ≥5 times that in humans receiving 0.5 mg/day (≥3 × the exposure at 1 mg/day). Tumor development was preceded by pneumocyte proliferation in the lung, which was not observed in rats, dogs, or monkeys, supporting the conclusion that lung tumors observed in mice are species-specific events not relevant to humans. Drug-related increased incidences of other types of tumors, including liver carcinomas in male mice, benign vascular tumors in female mice, brain gliomas in male and female rats, and liver adenomas and carcinomas in female rats, were seen only at high entecavir exposures [in mice approximately 70 times human exposure at 0.5 mg/day (approximately 40 times at 1 mg/day) and in rats 62 times (males) and 43 times (females) human exposure at 0.5 mg/day (35 and 24 times, respectively, at 1 mg/day)]; consequently, these tumor findings are unlikely to be relevant to humans.

No evidence of genotoxicity was observed in an Ames microbial mutagenicity assay, a mammalian-cell gene mutation assay, and a transformation assay with Syrian hamster embryo cells. Results of an oral micronucleus study and an oral DNA repair study in rats were also negative. Entecavir was clastogenic to human lymphocyte cultures at ≥2350 times the C_{max} in humans at 0.5 mg/day (approximately 1200 times at 1 mg/day).

In toxicology studies of entecavir in rodents and dogs, seminiferous tubular degeneration was observed at ≥62 and ≥35 times human exposure at 0.5 and 1 mg/day, respectively. No testicular changes were evident in a 1-year study in monkeys at exposures 296 times human exposure at 0.5 mg/day (167 times at 1 mg/day). There were no effects on fertility in male rats at exposures >160 times human exposure at 0.5 mg/day (>90 times at 1 mg/day). In female rats, no effects on fertility or early embryonic development were observed at exposures >165 times human exposure at 0.5 mg/day (>94 times at 1 mg/day).

Teratogenic Effects

In a developmental toxicity study in rats, entecavir demonstrated no selective developmental toxicity at exposures ≥50 times human exposure at 0.5 mg/day (≥28 times at 1 mg/day). Entecavir was a selective developmental toxicant in rabbits; however, at the

no-effect dose, exposure to entecavir was 377 times that in humans at 0.5 mg/day (210 times at 1 mg/day).

PHARMACEUTICAL PROPERTIES

List of Excipients

BARACLUDE® 0.5-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).

Shelf Life

24 months.

Do not use after the expiry date stated on the carton and on the blister pack.

Special Precautions for Storage

BARACLUDE® Tablets should be stored in the original package at temperatures not above 30°C.

Nature and Contents of Container

BARACLUDE® 0.5-mg film-coated tablets are white to off-white, triangular-shaped film-coated tablets, debossed with “BMS” on one side and “1611” on the other side. They are available in aluminum blister strips of 30’s in a carton.

Product Registration Holder

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