PRODUCT MONOGRAPH

[Pr] BARACLUDE*

(entecavir)

Tablets 0.5 mg

Oral Solution 0.05 mg/mL

Antiviral

Bristol-Myers Squibb Canada
Montreal, Canada

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 3
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 8
DRUG INTERACTIONS 11
DOSAGE AND ADMINISTRATION 13
OVERDOSAGE 14
ACTION AND CLINICAL PHARMACOLOGY 14
STORAGE AND STABILITY 23
DOSAGE FORMS, COMPOSITION AND PACKAGING 24

PART II: SCIENTIFIC INFORMATION 25
PHARMACEUTICAL INFORMATION 25
CLINICAL TRIALS 25
DETAILED PHARMACOLOGY 30
TOXICOLOGY 35
REFERENCES 46

PART III: CONSUMER INFORMATION 47
ABOUT THIS MEDICATION 47
WARNINGS AND PRECAUTIONS 47
INTERACTIONS WITH THIS MEDICATION 48
PROPER USE OF THIS MEDICATION 48
SIDE EFFECTS AND WHAT TO DO ABOUT THEM 49
HOW TO STORE IT 49

PrBARACLUDE*
(entecavir)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets 0.5 mg Solution 0.05 mg/mL	lactose monohydrate maltitol *For a complete listing, see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

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.

This indication is based on efficacy and safety data in nucleoside-treatment-naive and in lamivudine-refractory adult patients with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease and on more limited data in adult patients with HIV/HBV co-infection who have received prior lamivudine therapy.

CONTRAINDICATIONS

BARACLUDE is contraindicated in patients with previously demonstrated hypersensitivity to entecavir or any component of the product. **(For a complete listing, see Dosage Forms, Composition and Packaging section).**

WARNINGS AND PRECAUTIONS

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, re-initiation of anti-hepatitis B therapy may be warranted (see ADVERSE REACTIONS: Exacerbations of Hepatitis After Discontinuation of Treatment).

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including BARACLUDE, alone or in combination with antiretrovirals. Patients with decompensated liver disease may be at higher risk for lactic acidosis.

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 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: Patients co-infected with HIV and HBV)

General

BARACLUDE tablets contain lactose and are not recommended for patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. BARACLUDE Oral Solution is lactose-free and available as an alternative (see Dosage Forms, Composition and Packaging)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Positive carcinogenic results were found in two-year carcinogenicity studies with entecavir conducted in mice and rats. In male mice, increases in the incidences of lung adenomas were

observed at exposures ≥ 3 times the exposure in humans at 1 mg and lung carcinomas were observed in male and female mice at approximately 40 times the exposure in humans at 1 mg. Tumor development was preceded by pneumocyte proliferation in the lung, which was not observed in rats, dogs, or monkeys administered entecavir, indicating that a key event in lung tumor development observed in mice likely was species specific. Drug-related increased incidences of other types of tumors were seen at the highest entecavir exposures [in mice approximately 40 times and in rats 35 times (males) and 24 times (females) human exposure at 1 mg], including liver carcinomas in male mice, benign vascular tumors in female mice, brain microglial tumors in male and female rats, and liver adenomas and carcinomas in female rats. Skin fibromas were observed in female rats at both the high (0.4 mg/kg/day; equivalent to 4 times the exposure in humans at 1 mg) and highest (2.6 mg/kg/day; equivalent to 24 times the exposure in humans at 1 mg) doses. **(see TOXICOLOGY, Carcinogenesis, Mutagenesis, Impairment of Fertility for more detailed information).**

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

Entecavir was clastogenic to human lymphocyte cultures and in mouse lymphoma cells *in vitro.* Entecavir was not mutagenic in the Ames bacterial reverse mutation assay, 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 rats were administered entecavir at up to 30 mg/kg for up to 4 weeks, no evidence of impaired fertility was seen in males or females at systemic exposures >90 times those in humans at 1 mg. In rodent and dog toxicology studies, seminiferous tubular degeneration was observed at ≥ 35 times the exposure in humans at 1 mg. No testicular changes were evident in monkeys administered entecavir for 1 year at 167 times the exposure in humans at 1 mg.

Liver Transplant Recipients

The safety and efficacy of BARACLUDE in liver transplant recipients are unknown. The potential for pharmacokinetic interaction between entecavir and the immunosuppressants cyclosporine A or tacrolimus was not formally evaluated. If BARACLUDE treatment is determined to be necessary for a liver transplant recipient who has received or is receiving cyclosporine or tacrolimus, renal function must be carefully monitored both before and during treatment with BARACLUDE (see **ACTION AND CLINICAL PHARMACOLOGY: Special**

Populations and **DOSAGE AND ADMINISTRATION: Renal Impairment**).

Renal Impairment

BARACLUDE is predominantly eliminated by the kidney. Dosage adjustment of BARACLUDE is recommended for patients with a creatinine clearance <50 mL/min, including patients on hemodialysis or CAPD [continuous ambulatory peritoneal dialysis] (see **DOSAGE AND ADMINISTRATION: Renal Impairment**).

Special Populations

Patients co-infected with HIV and HBV

BARACLUDE has not been evaluated in patients who are co-infected with HIV and HBV and are not concurrently 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. Therefore therapy with BARACLUDE is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART). BARACLUDE has not been studied as a treatment for HIV infection and is not recommended for this use. (See ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Patients Co-infected with HIV and HBV and CLINICAL TRIALS: Special Populations, Patients Co-infected with HIV and HBV).

Before initiating BARACLUDE therapy, HIV antibody testing should be offered to all patients.

Pregnant Women

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.

Entecavir caused effects on embryo-fetal development in rats at doses that also produced maternal toxicity; at these doses, exposures to entecavir were 180 times those in humans at 1 mg. In rabbits, embryo-fetal toxicity was observed at exposures to entecavir 883 times those in humans at 1 mg. There were no adverse effects on growth, development, and reproductive performance in the progeny of rats administered entecavir at doses associated with exposures to

entecavir > 94 times those in humans at 1 mg. **(see TOXICOLOGY, Reproductive Toxicology for more detailed information).**

Pregnancy Registry:

To monitor maternal-fetal outcomes of pregnant women exposed to BARACLUDE a Pregnancy Registry has been established. To register patients, physicians must obtain prior consent. Physicians can register patients by calling 1-800-258-4263.

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.

Nursing Women

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

Pediatrics (<16 years of age)

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

Geriatrics (>65 years of age)

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: Renal Impairment)**.

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Assessment of adverse reactions is based on four pivotal studies (AI463014, AI463022, AI463026, and AI463027) in which 1720 patients with chronic hepatitis B 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 two years (Studies AI463022, AI463027 for nucleoside-naïve patients and studies AI463014, AI463026 for lamivudine-refractory patients). 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 patients 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 patients. (See WARNINGS AND PRECAUTIONS – Special Populations: Patients Co-infected with HIV and HBV)

The most common (≥ 3%) adverse events of any severity with at least a possible relation to study drug for BARACLUDE-treated patients were headache, fatigue, dizziness, and nausea. The most common adverse events among lamivudine-treated patients were headache, fatigue, and dizziness. One percent of BARACLUDE-treated patients in these four studies compared with 4% of lamivudine-treated patients discontinued for adverse events or abnormal laboratory test results.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical adverse reactions occurring in ≥ 3% of BARACLUDE-treated patients during therapy in four clinical studies in which BARACLUDE was compared with lamivudine, in addition to selected clinical adverse reactions that occurred in < 3% of patients are presented in Table 1.

Table 1:Clinical Adverse Reactions Reported in ≥ 3% of BARACLUDE-treated Patients, Plus Selected Clinical Adverse Reactions in Four BARACLUDE Clinical Trials – Through 2 Years of Treatment

Body System/ Adverse Event [a]	**Nucleoside-Naive**[b]		**Lamivudine-Refractory**[c]	
	BARACLUDE 0.5 mg n = 679 %	**Lamivudine 100 mg n = 668 %**	**BARACLUDE 1 mg n = 183 %**	**Lamivudine 100 mg n = 190 %**
Gastrointestinal				
Nausea	3	2	4	3
Abdominal pain upper	3	2	2	5
Dyspepsia	2	2	3	<1
Diarrhea	1	<1	2	1
Vomiting	1	<1	1	<1
General				
Fatigue	5	5	9	6
Nervous System				
Headache	8	8	10	7
Dizziness	4	3	5	2
Somnolence	1	1	2	1
Psychiatric				
Insomnia	2	1	1	<1

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

b Studies AI463022 and AI463027 Mean duration of therapy was 69 weeks for BARACLUDE-treated and 63 weeks for lamivudine-treated patients.

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 patients who experienced recurrent viremia on lamivudine therapy. Mean duration of therapy was 73 weeks for BARACLUDE-treated and 51 weeks for lamivudine-treated patients.

Exacerbations of Hepatitis After Discontinuation of Treatment

In the Phase 3 studies, a subset of patients was allowed to discontinue treatment at or after 52 weeks if they achieved a protocol-defined response to therapy. An exacerbation of hepatitis or ALT flare was defined as ALT >10 X ULN and >2 X the patient's reference level (minimum of the baseline or last measurement at end of dosing). As demonstrated in Table 2, a proportion of patients experienced post-treatment ALT flares. If BARACLUDE is discontinued without regard to treatment response, the rate of post-treatment flares could be higher.

Table 2: Exacerbations of Hepatitis During Off-Treatment Follow-up, Patients in Studies AI463022 , AI463027 and AI463026

	Patients with ALT Elevations > 10xULN and >2 x Reference[a]	
	BARACLUDE	**Lamivudine**
Total Nucleoside-naïve HBeAg-positive HBeAg-negative	28/476 (6%) 4/174 (2%) 24/302 (8%)	43/417 (10%) 13/147 (9%) 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.

Abnormal Hematologic and Clinical Chemistry Findings

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 BARACLUDE Clinical Trials -Through 2 Years

Test	Nucleoside -Naive[b]		Lamivudine-Refractory[c]	
	BARACLUDE 0.5 mg (n = 679)	**Lamivudine 100 mg (n = 668)**	**BARACLUDE 1 mg (n = 183)**	**Lamivudine 100 mg (n = 190)**
ALT> 10 x ULN and > 2 x baseline	2%	4%	2%	11%
ALT > 5.0 ULN	11%	16%	12%	24%
AST > 5.0 ULN	5%	8%	5%	17%
Albumin < 2.5 g/dL	<1%	<1%	0%	2%
Total bilirubin > 2.5 x ULN	2%	2%	3%	2%
Amylase > 2.1 x ULN	2%	2%	3%	3%
Lipase > 2.1 x ULN	7%	6%	7%	7%
Creatinine 3.0 x ULN	0%	0%	0%	0%
Confirmed creatinine increase ≥ 44.2 mmol/L	1%	1%	2%	1%
Hyperglycemia fasting >13.8 mmol/L	2%	1%	3%	1%
Glycosuria[d]	4%	3%	4%	6%
Hematuria[e]	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 ≥ 44.2 mmol/L and ALT >10 X ULN and >2 X baseline.

[b] Studies AI463022 and AI463027. . Mean duration of therapy was 69 weeks for BARACLUDE-treated and 63 weeks for lamivudine-treated patients.

[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 patients who experienced recurrent viremia on lamivudine therapy. Mean duration of therapy was 73 weeks for BARACLUDE-treated and 51 weeks for lamivudine-treated patients.

[d] Grade 3=3+, large, ≥ 500 mg/dL; Grade 4=4+, marked, severe

[e] Grade 3=3+, large, Grade 4 =≥ 4+, marked, severe, many

ULN= upper limit of normal

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

Post-Market Adverse Drug Reactions

The following events have been identified during postapproval use of BARACLUDE. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made, as well, the existence of underlying medical conditions confounds the assessment of causality.

Gastrointestinal disorders: upper abdominal pain

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

Hepatobiliary disorders: increased transaminases

Skin and subcutaneous tissue disorders: alopecia, rash

Blood and lymphatic system disorders: leukopenia, neutropenia, platelet count decreased

Gastrointestinal disorders: pancreatitis

Immune System Disorders: hypersensitivity and drug hypersensitivity including anaphylactoid reaction

DRUG INTERACTIONS

Overview

Since entecavir is primarily eliminated by the kidneys (see **ACTION AND CLINICAL PHARMACOLOGY: Metabolism and Elimination**), 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. In clinical trials, coadministration of BARACLUDE 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.

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. (See **ACTION AND CLINICAL PHARMACOLOGY: Metabolism and Elimination**.) 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 BARACLUDE.

Drug-Drug Interactions

In clinical studies, the steady-state pharmacokinetics of BARACLUDE and coadministered drug were not altered in interaction studies of entecavir with lamivudine, adefovir dipivoxil, and tenofovir disoproxil fumarate.

Drug-Food Interactions

Oral administration of 0.5 mg of BARACLUDE 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 hour fed vs. 0.75 hours fasted), a decrease in C_{max} of 44%-46%, and a decrease in AUC of 18%-20%. Therefore, BARACLUDE should be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

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

For adults and adolescents 16 years of age or older with a history of hepatitis B viremia while receiving lamivudine or with known lamivudine resistance mutations, the recommended dose of BARACLUDE is 1 mg (two 0.5 mg tablets) once daily.

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

BARACLUDE 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.

Renal Impairment

In patients with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased. Dosage adjustment is recommended for patients with creatinine clearance <50 mL/min, including patients on hemodialysis or CAPD (continuous ambulatory peritoneal dialysis), as shown in Table 4.

Table 4: 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] On hemodialysis days, administer after hemodialysis.

Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

Duration of Therapy

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

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended. 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Entecavir is a guanosine nucleoside analogue that is efficiently phosphorylated to the active triphosphate form and exhibits selective activity against HBV polymerase, competes with the natural substrate deoxyguanosine triphosphate, and inhibits all three functional 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 has an inhibition constant (Ki) for HBV DNA polymerase of

0.0012 μM and is a weak inhibitor of cellular DNA polymerases α, ß, 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).

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} 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 M184I substitution showed loss of susceptibility to entecavir.

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 vitro*, 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 *in vitro* 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.

Drug Resistance

Clinical Studies

In nucleoside-naive studies (AI463022, AI463027, and rollover study AI463901) and in studies of lamivudine-refractory HBV (AI463026, AI463014, AI463015, and rollover study AI463901), patients 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 are observed in

viruses which harbour primary lamivudine resistance substitutions (M204I/V ± L180M) along with additional substitutions at residues T184, S202 or M250 of the viral polymerase.

Nucleoside-naïve patients:

Through Year 5, genotypic evidence of entecavir resistance (ETVr) substitutions at residues T184, S202 or M250 was observed in 3 patients (<1%), 2 of whom experienced virologic breakthrough (see Table 5). The results reflect use of a 1 mg dose of entecavir in 147 patients in Year 3 and all patients in Years 4 and 5 and of entecavir-lamivudine combination therapy (followed by long-term entecavir monotherapy) for a median of 20 weeks for 130 patients in Year 3 and for 1 week for one patient in Year 4 in a rollover study.

Table 5: Genotypic Entecavir Resistance and Virologic Breakthrough with Resistance Through Year 5, Nucleoside-Naïve Studies

	Year 1	Year 2	Year 3[a]	Year 4[a]	Year 5 [a]
Subjects treated and monitored for resistance[b]	663	278	149	121	108
Emerging Genotypic ETV[c,d]	1	1	1	0	0
Genotypic ETVr [c,d] withVirologic 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%
Cumulative probability of genotypic ETVr [c,d] with virologic breakthrough[e]	0.2%	0.2%	0.8%	0.8%	0.8%

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

[b]Includes subjects 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 T184, S202 or M250.

[d]Subjects 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 point.

Emerging amino acid substitutions at M204I/V ± L180M, L80I, or V173L, which conferred decreased phenotypic susceptibility to entecavir in the absence of S202, T184, or M250 changes, were detected in the HBV of 3 patients (3/663 = <1%) who experienced virologic breakthrough by the end of Year 5.

Lamivudine-refractory patients:

Through Year 5, genotypic evidence of entecavir resistance (ETVr) substitutions at residues T184, S202 or M250 was observed in 47 patients, 39 of whom experienced virologic breakthrough (see Table 6) The results reflect the use of entecavir-lamivudine combination therapy (followed by long-term entecavir monotherapy) for a median of 13 weeks for 48 patients in Year 3, for 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.

Table 6: Genotypic Entecavir Resistance and Virologic Breakthrough with Resistance Through Year 5, Lamivudine-Refractory Studies

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

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

[b]Includes subjects 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 T184, S202 or M250.

[d]Subjects 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 point.

[f]ETVr occurring in any year, virologic breakthrough in a 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 they can exist at a low frequency before entecavir treatment. Through Year 5, 3 of the 10 patients experienced virologic breakthrough. Isolates from patients who experienced virologic breakthrough with the emergence of S202, T184 and/or M250 substitutions (n=39), had a median 285 fold-change in entecavir susceptibility as compared to wild type HBV. Three additional subjects experienced virologic breakthrough with the emergence of M204I/V ± L180M, L80V or V173L/M alone.

Cross-resistance

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, HBV containing lamivudine resistance substitutions M204V/I +/- L180M was 8-fold less susceptible to entecavir than wild type virus. Further reductions (>70 fold) in entecavir phenotypic susceptibility required the presence of primary lamivudine resistance amino acid substitutions (M204V/I +/- L180M) 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.

Recombinant HBV genomes encoding adefovir resistance-associated substitutions at either rtN236T or rtA181V remained susceptible to entecavir. HBV isolates from lamivudine-refractory patients failing BARACLUDE therapy were susceptible *in vitro* to adefovir but retained resistance to lamivudine.

Pharmacokinetics

The single- and multiple-dose pharmacokinetics of entecavir were evaluated in healthy subjects

and patients with chronic hepatitis B infection (including liver transplant recipients). Steady-state Pharmacokinetics of entecavir are summarized in Table 7.

Table 7 - Summary of Entecavir Pharmacokinetic Parameters in Healthy Subjects

	Cmax (ng/mL)	$T_{1/2}$ (h)	AUC(TAU)[1] (ng.h/mL)	Clearance (CLT/F) (mL/min)	CLR (mL/min)
Steady-state mean (0.5 mg)	4.2	130	14.8	572	360
Steady-state mean (1.0 mg)	8.2	149	26.4	636	471

[1] Geometric mean

Absorption

Following oral administration in healthy subjects, entecavir was rapidly absorbed with peak plasma concentrations occurring 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 6-10 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.

A bioavailability study was performed on 24 healthy subjects under fasting conditions comparing the rate and extent of absorption of a 10 mL single oral dose of entecavir 0.05 mg/mL oral solution and a single oral dose of entecavir 0.5 mg tablet. Results showed that the bioavailability following administration of the 0.05 mg/mL oral solution was comparable to the bioavailability following administration of the 0.5 mg tablet. (see CLINICAL TRIALS for further details).

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

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. Protein binding to human serum protein *in vitro* was approximately 13%.

Metabolism

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 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 were observed. Minor amounts of the phase II metabolites glucuronide and sulfate conjugate were observed.

Excretion

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, indicating 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**).

Special Populations and Conditions

Patients Co-Infected with HIV and HBV

Study AI463038 was a randomized, double-blind, placebo-controlled study of BARACLUDE versus placebo in 68 patients co-infected with HIV and HBV, who experienced recurrence of

HBV viremia while receiving a lamivudine-containing highly active antiretroviral (HAART) regimen. Patients continued their lamivudine-containing HAART regimen (lamivudine dose 300 mg/day) and were assigned to add either BARACLUDE 1 mg once daily (51 patients) or placebo (17 patients) for 24 weeks followed by an open-label phase for an additional 24 weeks where all patients received BARACLUDE. At baseline, patients had a mean serum HBV DNA level by PCR of 9.13 log $_{10}$ copies /mL. Ninety-nine percent of patients 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 Table8. 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 – Special Populations: Patients Co-Infected with HIV and HBV)

Table 8: 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 patients also received a lamivudine-containing HAART regimen

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

[c] Percentage of patients 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 patients originally assigned to BARACLUDE, at the end of the open-label phase (Week 48), 8% of patients 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 patients with abnormal ALT at baseline had ALT normalization (≤ 1 X ULN).

Pediatrics

Pharmacokinetic studies have not been conducted in children.

Geriatrics

The effect of age on the pharmacokinetics of entecavir was evaluated following administration of a single 1mg oral dose in healthy young (20–40 years old) and elderly (65-83 years old) 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: Renal Impairment**).

Gender / race

There are no significant gender/racial differences in entecavir pharmacokinetics.

Hepatic Impairment

No dosage adjustment of BARACLUDE is recommended for patients with hepatic impairment.

The pharmacokinetics of entecavir following a single 1 mg dose were studied in patients (without chronic hepatitis B infection) with moderate and severe hepatic impairment. The pharmacokinetics of entecavir were similar between hepatically impaired patients and healthy control subjects.

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 patients. The potential for pharmacokinetic interactions between entecavir and cyclosporine A or tacrolimus was not formally evaluated. Renal function must be carefully monitored both before and during treatment with BARACLUDE in liver transplant recipients who have received or are receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus (see **DOSAGE AND ADMINISTRATION: Renal Impairment**).

Renal Insufficiency

The pharmacokinetics of entecavir following a single 1 mg dose were studied in patients (without chronic hepatitis B infection) with selected degrees of renal impairment, including patients whose renal impairment was managed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Results are shown in Table 9.

Table 9: Pharmacokinetic Parameters in Subjects with Selected Degrees of Renal Function

	Baseline Creatinine Clearance (mL/min)				Severe Managed with Hemodialysis[a] (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·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.

Dosage adjustment is recommended for patients with a creatinine clearance <50 mL/min, including patients on hemodialysis or CAPD. (See **DOSAGE AND ADMINISTRATION: Renal Impairment**).

Following a single 1 mg dose of BARACLUDE, hemodialysis removed approximately 13% of the BARACLUDE dose over 4 hours and CAPD removed approximately 0.3% of the dose over 7 days. BARACLUDE should be administered after hemodialysis.

STORAGE AND STABILITY

BARACLUDE Tablets should be stored in a tightly closed container at 25° C; excursions permitted between 15-30° C.

BARACLUDE Oral Solution should be stored at 25° C; excursions permitted between 15-30° C. Protect from light. Store bottle in outer carton. 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BARACLUDE (entecavir) film-coated tablets and oral solution contain entecavir as the active ingredient.
BARACLUDE 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.

BARACLUDE oral solution contains the following inactive ingredients: maltitol, sodium citrate, citric acid, methylparaben, propylparaben, and orange flavour.

BARACLUDE 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
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 90 tablets
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

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. Patients should be instructed to hold the 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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

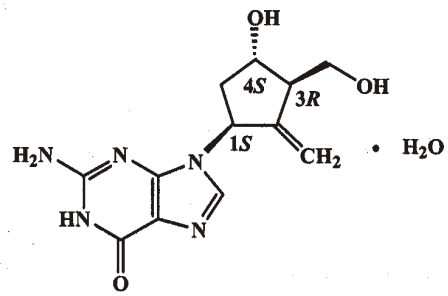
Drug Substance

Proper name: Entecavir

Chemical name: 2-amino-1,9-dihydro-9-[(*1S,3R,4S*)-4-hydroxy-3-(hydroxymethyl)-2- methylenecyclopentyl]- 6*H*-purin-6-one, monohydrate.

Molecular formula and molecular mass: $C_{12}H_{15}N_5O_3 \bullet H_2O$ 295.3

Structural formula:



Physicochemical properties: 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.

CLINICAL TRIALS

The safety and efficacy of BARACLUDE were evaluated in three pivotal active-controlled trials on five continents. These studies included 1633 patients 16 years of age or older with chronic hepatitis B 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 ≥ 1.3 times the upper limit of normal (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 patients co-infected with HBV and HIV.

Nucleoside-Naive Patients With Compensated Liver Disease, Outcomes at 48 Weeks

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-naive patients with chronic hepatitis B infection and detectable HBeAg. The mean age of patients was 35 years, 75% were male, 57% were Asian, 40% were Caucasian, and 13% had previously received interferon-α. At baseline, patients 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 was 143 U/L. Paired, adequate liver biopsy samples were available for 89% of patients.

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-naive patients with HBeAg-negative (HBeAb-positive) chronic hepatitis B infection. The mean age of patients was 44 years, 76% were male, 39% were Asian, 58% were Caucasian, and 13% had previously received interferon-α. At baseline, patients 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 patients.

In Studies AI463022 and AI463027, BARACLUDE was superior to lamivudine on the primary efficacy endpoint of Histologic Improvement, defined as ≥ 2-point 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 10. Biochemical, virologic, and serologic outcome measures are shown in Table 11.

Table 10: Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Nucleoside-Naive Patients 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]**	**Difference BARACLUDE Lamivudine (95% CI) [b]**	**BARACLUDE 0.5 mg n = 296[a]**	**Lamivudine 100 mg n = 287[a]**	**Difference BARACLUDE Lamivudine (95% CI)[b]**
Histologic Improvement (Knodell Scores)						
Improvement[c]	72%	62%	9.9% (2.6%, 17.2%) *p < 0.01*	70%	61%	9.6% (2.0%, 17.3%) *p < 0.05*
No improvement	21%	24%		19%	26%	
Ishak Fibrosis Score[d]						
Improvement[d]	39%	35%	3.2% (-4.4%, 10.7%) *p= NS[e]*	36%	38%	-1.8% (-9.7%, 6.0%) *p= NS[e]*
No change	46%	40%		41%	34%	
Worsening[d]	8%	10%		12%	15%	
Missing Week 48 biopsy	7%	14%		10%	13%	

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

[b] In these analyses, missing or inadequate biopsies at Week 48 were classified "no improvement."

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

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

[e] NS = Not significant.

Table 11: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Nucleoside-Naive Patients in Studies AI463022 and AI463027

	Study AI463022 (HBeAg-Positive)			Study AI463027 (HBeAg-Negative)		
	BARACLUDE 0.5 mg n = 354	**Lamivudine 100 mg n = 355**	**Difference BARACLUDE Lamivudine (95% CI)**	**BARACLUDE 0.5 mg n = 325**	**Lamivudine 100 mg n = 313**	**Difference BARACLUDE Lamivudine (95% CI)**
ALT normalization (≤ 1.0X ULN)	68 %	60 %	8.4 % 1.3%, 15.4% *p = 0.0202*	78 %	71%	6.9 %[a] 0.2, 13.7 *p = 0.0451*
HBV DNA Mean change from baseline by PCR[a] (log_{10} copies/mL)	-6.86	-5.39	-1.5 (-1.8 -1.3) *p < 0.0001*	-5.04	-4.53	-0.4 (-0.6 -0.3) *p < 0.0001*
Proportion undetectable (< 300 copies/mL) by PCR[a, b]	67%	36%	30.3% (23.3%-37.3%) *p < 0.0001*	90%	72%	18.3% (12.3%, 24.2%) *p < 0.0001*
<0.7 MEq/mL by bDNA [c]	91%	65%	25.6% (19.8%, 31.4%) *p < 0.0001*	95%	89%	5.9% (1.8%, 10.1%) *p < 0.01*
Loss of HBeAg	22%	20%		N/A	N/A	
HBeAg seroconversion	21%	18%		N/A	N/A	

[a] Roche COBAS Amplicor PCR assay.

[b] At Week 24, HBV DNA <300-copies/mL by PCR was observed in 42% of BARACLUDE-treated patients and 25% of lamivudine-treated patients (p<0.0001) in Study AI463022 and 74% of BARACLUDE -treated patients and 62% of lamivudine-treated patients (p = 0.0013) in Study AI463027.

[c] Quantiplex bDNA assay.

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

Lamivudine-Refractory Patients, Outcomes at 48 Weeks

Study AI463026 was a multinational, randomized, double-blind study of BARACLUDE in 286 (of 293 randomized) HBeAg-positive patients with lamivudine-refractory chronic hepatitis B infection. Patients 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 patients 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, patients 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 patients.

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 12. Table 13 shows selected virologic, biochemical, and serologic endpoints.

Table12: Histologic Improvement and Change in Ishak Fibrosis Score, and Composite Endpoint at Week 48, Lamivudine-Refractory Patients in Study AI463026

	Study AI463026 (HBeAg-Negative)		
	BARACLUDE 1 mg n = 124[a]	**Lamivudine 100 mg n = 116[a]**	**Difference BARACLUDE Lamivudine (97.5% CI)**
Histologic Improvement (Knodell Scores)			
Improvement[b]	55%	28%	27.3%[c] (13.6%, 40.9%) *p < 0.0001*
No improvement	34%	57%	
Ishak Fibrosis Score			
Improvement[d]	34%	16%	17.5%[c] (6.8%, 28.2%)[e] *p < 0.01*
No change	44%	42%	
Worsening[d]	11%	26%	
Inadequate Week 48 biopsy	2%	1%	
Missing Week 48 biopsy	10%	15%	

[a] Patients 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] In this analysis, missing or inadequate biopsies at Week 48 were classified "no improvement."

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

[e] 95% confidence interval.

Table 13: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Lamivudine-Refractory Patients in Study AI463026

	Study AI463026		
	BARACLUDE 1 mg n = 141	**Lamivudine 100 mg n = 145**	**Difference BARACLUDE Lamivudine (95% CI)**
ALT normalization (≤ 1.0 X ULN)[a]	61%	15 %	45.8 %[b] (35.9 %, 55.8 %) *p < 0.0001*
HBV DNA Mean change from baseline by PCR [a] (log_{10} copies/mL)	-5.1	-0.48	-4.4 [a] (-4.8, -4.0)
Proportion undetectable (< 300 copies/mL by PCR[a])	19%	1%	17.8% (11.0, 24.5) *p < 0.0001*
<0.7 MEq/mL by bDNA[c]	66%	6%	60.4%[a] (51.8%, 69.1%) *p < 0.0001*
Loss of HBeAg	10%	3%	
HBeAg seroconversion	8%	3%	

[a] Roche COBAS Amplicor PCR assay.
[b] At Week 24, HBV DNA <300copies/mL by PCR was observed in 7% of BARACLUDE-treated patients and no lamivudine-treated patients (p=0.0011) in Study AI463026
[c] Quantiplex bDNA assay.

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

Outcomes Beyond 48 Weeks

The optimal duration of therapy with BARACLUDE is unknown. According to protocol-mandated criteria in the Phase 3 clinical trials, patients 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 patients) or ALT <1.25 X ULN (in HBeAg-negative patients) at Week 48. Patients who achieved virologic suppression but did not have a serologic response (HBeAg-positive) or did not achieve ALT <1.25 X ULN (HBeAg-negative) continued blinded dosing through 96 weeks or until response was achieved. These protocol-specified patient management guidelines are not intended as guidance for clinical practice.

Nucleoside-naive, outcomes beyond 48 weeks: Cumulative confirmed outcomes through Week 96 for all treated patients in studies of nucleoside-naive patients are shown in Table 14.

Table 14: Outcomes Through 96 Weeks, Nucleoside-Naïve Patients in Studies AI463022 and AI463027 (All Treated)

	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)	80%*	39%	94%*	77%
ALT normalization (≤ 1xULN)	87%*	79%	89%	84%
HBeAg seroconversion[b]	31%	26%	NA	NA
HBeAg loss[b]	5%	3%	<1%	<1%

a Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).
b through the last observation on or off treatment.
* p<0.01

Among nucleoside-naive HBeAg-positive patients, 243 BARACLUDE-treated and 164 lamivudine-treated patients continued blinded treatment into year 2 (median duration of therapy was 96 weeks). The proportion of patients with HBV DNA <300 copies/mL by PCR increased from 64% at Week 48 to 81% at Week 96/EOD [End of Dosing (last observation carried forward) for patients who discontinued between Weeks 48 and 96] for BARACLUDE-treated patients and remained stable for lamivudine-treated patients (40% at Week 48 and 39% at Week 96/EOD). For BARACLUDE-treated patients, ALT normalization (≤1 X ULN) occurred in 66% at Week 48 and 79% at Week 96/EOD. The percentage of lamivudine-treated patients with ALT normalization was 71% at Week 48 and 68% at Week 96/EOD.

Among nucleoside-naive HBeAg-negative patients, 26 patients continued BARACLUDE treatment and 28 patients continued lamivudine treatment into year 2 (median duration of therapy was 96 weeks). The proportion of patients with HBV DNA <300 copies/mL remained stable in both treatment groups (BARACLUDE 100% at Week 48 and 96% at Week 96/EOD; lamivudine 64% at both Week 48 and Week 96/EOD). No patient in either treatment group had ALT normalization at Week 48, while 27% of BARACLUDE-treated patients and 21% of lamivudine-treated patients achieved ALT normalization at Week 96/EOD.

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 10, footnote c) 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 X ULN.

Lamivudine-refractory, outcomes beyond 48 weeks: Cumulative confirmed outcomes through Week 96 for all treated lamivudine-refractory patients are shown in Table 15.

Table 15: Outcomes Through 96 Weeks, Lamivudine Refractory Patients in Study AI463026 (All Treated)

	BARACLUDE 1 mg n= 141	**LAMIVUDINE 100 mg n=145**
HBV DNA[a]		
Proportion undetectable (<300 copies/mL)	30%*	<1%
ALT normalization (≤ 1 x ULN)	85%*	29%
HBeAg seroconversion[b]	17%*	6%

a Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).
b through the last observation on or off treatment.
*p<0.01

Among lamivudine-refractory patients in Study AI463026, 77 BARACLUDE-treated patients continued dosing into year 2 (median duration of therapy was 96 weeks). The proportion of patients with HBV DNA <300 copies/mL increased from 21% at Week 48 to 40% at Week 96/EOD. The proportion of patients with ALT normalization increased from 65% at Week 48 to 81% at Week 96/EOD.

Post-Treatment Follow-up

For the 31% of nucleoside-naive, HBeAg-positive BARACLUDE-treated patients who met response criteria (virologic suppression by bDNA assay and loss of HBeAg) and discontinued therapy, response was sustained throughout the 24-week post-treatment follow-up period in 75%. For the 88% of nucleoside-naive, HBeAg-negative BARACLUDE-treated patients who met response criteria (virologic suppression by bDNA assay and ALT <1.25 X ULN), response was sustained throughout the 24-week post-treatment follow-up period in 46%. 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 throughout the 24-week post-treatment follow-up period in 11 (50%).

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 patients co-infected with HIV and HBV who experienced recurrence of HBV viremia while receiving a lamivudine-containing highly active antiretroviral (HAART) regimen. Patients continued their lamivudine-containing HAART regimen (lamivudine dose 300 mg/day) and were assigned to add either BARACLUDE 1 mg once daily (51 patients) or placebo (17 patients) for 24 weeks followed by an open-label phase for an additional 24 weeks where all patients received BARACLUDE. At baseline, patients had a mean serum HBV DNA level by PCR of 9.13 $\log_{10}$ copies/mL. Ninety-nine percent of patients 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 Table16. 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 – Special Populations: Patients Co-infected with HIV and HBV).

Table 16: 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 patients also received a lamivudine-containing HAART regimen

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

[c] Percentage of patients 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 patients originally assigned to BARACLUDE, at the end of the open-label phase (Week 48), 8% of patients 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 patients with abnormal ALT at baseline had ALT normalization (≤ 1% ULN).

Comparative Bioavailability Studies

A bioavailability study was performed on 24 healthy male and female volunteers under fasting conditions comparing the rate and extent of absorption of a 10 mL single oral dose of entecavir 0.05 mg/mL oral solution and a single oral dose of entecavir 0.5 mg tablet. The results from the study are summarized below in Table 17.

Table 17: Summary Table of the Comparative Bioavailability Data
Entecavir
(A single 0.5 mg Dose: 10 mL of a 0.05 mg/mL oral solution versus 0.5 mg tablets)
From Measured Data
Geometric Mean
Arithmetic Mean (CV%)

Parameter[a]	Entecavir 0.05 mg/mL Oral Solution	Entecavir 0.5 mg Tablet	Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (ng·h/mL)	10.89 11.17 (26)	11.06 11.25 (20)	0.987	(0.958, 1.018)
C_{max} (ng/mL)	3.66 3.77 (27)	3.79 3.88 (23)	0.968	(0.918, 1.021)
T_{max}[b](h)	0.50 (0.25, 1.00)	0.50 (0.50, 1.00)		

[a] Due to the nature of the active ingredient (long half-life) and the design of the study, AUC and $T_{1/2}$ could not be accurately estimated; therefore, they are not reported.

[b] Median (min, max)

DETAILED PHARMACOLOGY

Mechanism of Action

Entecavir is a guanosine nucleoside analogue that is efficiently phosphorylated to the active triphosphate form and exhibits selective activity against HBV polymerase. Entecavir triphosphate competes with the natural substrate deoxyguanosine triphosphate, and inhibits all three functional 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 has an inhibition constant (Ki) for HBV DNA polymerase of 0.0012 μM and is a weak inhibitor of cellular DNA polymerases α, ß, 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).

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} 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 M184I substitution showed loss of susceptibility to entecavir.

Daily or weekly entecavir treatment significantly reduced viral DNA levels (4 to 8 $\log_{10}$) in two relevant animal models, woodchucks chronically infected with woodchuck hepatitis virus (WHV) and ducks infected with duck HBV. Long-term studies in woodchucks demonstrated that oral weekly dosing of 0.5 mg/kg entecavir (similar exposure to the 1 mg human dose) maintained viral DNA levels at undetectable levels (<200 copies/mL by PCR) for up to 3 years in 3 of 5 woodchucks. No entecavir resistance changes were detected in the HBV polymerase in any of the treated animals for up to 3 years of treatment.

TOXICOLOGY

Acute Toxicity (Table 1)

Single-dose oral toxicity studies with entecavir were conducted in mice and rats at doses ranging from 40 to 5000 mg/kg. In mice, no drug-related changes were noted at 40 mg/kg. Body-weight losses were noted at ≥ 200 mg/kg. At ≥1000 mg/kg, signs of overt toxicity and deaths were observed. In rats, no drug-related changes were observed at doses of 40 or 200 mg/kg. Deaths occurred at ≥ 1000 mg/kg.

Repeat-Dose Toxicity (Table 2)

Repeat-dose studies utilizing once daily oral dosing were conducted in mice, rats, dogs, and monkeys. Pivotal studies included two 6-month oral studies each in mice and rats to assess chronic toxicity and to aid in the selection of doses for oral carcinogenicity studies; two 3-month studies in dogs to assess toxicity and reversibility of drug-related changes, and a 1-year toxicity study in monkeys that included a 3-month interim evaluation.

In dogs, species-specific, reversible CNS inflammation was observed at doses that achieved ≥ 51 times the exposure to entecavir in humans at 1 mg. The species-specificity, reversibility, and high exposure multiples at which the CNS inflammation was observed suggest that this finding is not relevant to human safety. Other target organs in repeat-dose studies in animals were the kidneys, liver, lungs, skeletal muscle and testis; the changes in these organs were considered unlikely to be relevant to human safety because they were either species-specific, associated with high exposure multiples relative to humans, and/or, in clinical trials with entecavir, they were not target tissues. With regard to target-organ toxicity in general, the results of a 1-year study in monkeys were most compelling because no target organ toxicity was evident at ≥ 136 times the exposure to entecavir in humans at 1 mg.

Reproductive Toxicology (Table 3)

Reproductive toxicology studies were conducted with entecavir to assess potential effects on embryonic and fetal development in rats and rabbits and on growth, development, and reproductive performance of progeny in rats.

In rats and rabbits, no embryotoxicity or maternal toxicity was observed at 28 and 212 times, respectively, the exposure to entecavir at 1 mg in humans. In rats, maternal toxicity, embryo-fetal toxicity (resorptions), and associated decreases in live-litter size occurred at 180 times the exposure in humans at 1 mg. Additional findings in rat fetuses at 3100 times the exposure in humans at 1 mg included lower body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternebrae, and phalanges), and extra lumbar vertebrae and ribs. In rabbits, embryo-fetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed at 883 times the exposure in humans at 1 mg. In a peri-

postnatal study in rats, no adverse effects on offspring were seen at > 94 times the exposure in humans at 1 mg.

Carcinogenesis, Mutagenesis, Impairment of Fertility (Tables 4 & 5)

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 1 mg.

MICE: Lung adenomas were increased in males and females at exposures 3 and 40 times those in humans at 1 mg, respectively. Lung carcinomas in both male and female mice were increased at exposures approximately 40 times those in humans at 1 mg. Lung tumor development was preceded by pneumocyte proliferation in the lung, which was not observed in rats, dogs, or monkeys administered entecavir, indicating that a key event in lung tumor development observed in mice likely was species specific. At the highest dose level tested (equivalent to approximately 40 times the exposure in humans at 1 mg) hepatocellular carcinomas and the combined incidence of adenomas and carcinomas in male mice and vascular tumors (hemangiomas of ovaries and uterus and hemangiomas/hemangiosarcomas of spleen) in female mice were significantly increased.

The NOEL for neoplasia was 0.004 mg/kg/day for males (equivalent to 1-times the exposure in humans at 1 mg), based on pulmonary adenomas; for all other tumors in male and female mice the NOEL was 0.4 mg/kg (equivalent to 14 and 11 times the exposure in humans at 1 mg for male and female mice, respectively). At tumorigenic doses, systemic exposures were 3-times (pulmonary tumors in male mice) and approximately 40-times (all other tumors) that in humans at 1 mg daily.

RATS: In female rats, hepatocellular adenomas and the combined incidence of adenomas and carcinomas were significantly increased at the highest dose level, equivalent to 24-times the exposure in humans at 1 mg. Brain microglial tumors were significantly increased in both male and female rats at the highest dose, equivalent to 35 and 24 times exposure in humans at 1 mg respectively. Skin fibromas in female rats were significantly increased at the 0.4 (high) and 2.6 mg/kg/day (highest) doses, equivalent to 4 and 24 times exposure in humans at 1 mg respectively.

The NOEL for neoplasia was 0.2 mg/kg/day for males (equivalent to 5 times the exposure in humans at 1 mg) and for females 0.06 mg/kg/day based on skin fibromas (equivalent to < 1 times the exposure in humans at 1 mg) or 0.4 mg/kg/day (all other tumors, equivalent to 4 times the exposure in humans at 1 mg). At tumorigenic doses, systemic exposures were 35 and 4/24 times that in humans at 1 mg in male and female rats, respectively.

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

Entecavir was clastogenic to human lymphocyte cultures and in mouse lymphoma cells *in vitro.* Entecavir was not mutagenic in the Ames bacterial reverse mutation assay, 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 rats were administered entecavir at up to 30 mg/kg for up to 4 weeks, no evidence of impaired fertility was seen in males or females at systemic exposures >90 times those in humans at 1 mg. In rodent and dog toxicology studies, seminiferous tubular degeneration was observed at ≥ 35 times the exposure in humans at 1 mg. No testicular changes were evident in monkeys administered entecavir for 1 year at 167 times the exposure in humans at 1 mg.

Table 1 - ACUTE TOXICITY

Species/ Strain	N/Dose/ Sex	Dose mg/kg/day	Route of Administration	Observed Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Findings
Mouse/CD-1	M5 F5	0, 40, 200, 1000, & 5000	Oral, gavage	200	≥ 1000	40 mg/kg: No drug-related findings. ≥ 200 mg/kg: Transient body-weight losses. ≥ 1000 mg/kg: One male at 1000 mg/kg and 4 males and all females at 5000 mg/kg died. In the testis, moderate degeneration of seminiferous tubular epithelium. In the spleen, mild to moderate lymphoid depletion.
Rat/SD	M5	0, 40, 200, 1000, & 5000	Oral, gavage	200	≥ 1000	≤ 200 mg/kg: No drug-related findings. ≥ 1000 mg/kg: One rat at 1000 mg/kg and all rats at 5000 mg/kg died. In rats that died, red discoloration of small intestine associated with hemorrhage, and necrosis of duodenum and jejunum.

Table 2 – REPEAT-DOSE TOXICITY

Species/Strain	N/Sex	Dose mg/kg/day	Route of Administration	Duration of Dosing	NOAEL (mg/kg)	Findings
MOUSE						
Mouse/CD-1	Four groups of 10M 10F each	0, 0.2, 1, & 5	Oral, gavage	6 months	< 0.2	≥ 0.2 mg/kg: In the liver, minimal to moderate centrilobular degeneration. ≥ 1 mg/kg: In the lung, minimal to mild alveolar histiocytosis. In skeletal muscle, minimal to mild myopathy. 5 mg/kg: Lower body weight (males); minimal to moderate decreases in total leukocyte and lymphocyte counts; mild to moderate increases in serum ALT and/or AST; increased kidney and decreased testes weights in males; and minimal to mild centrilobular hepatocellular hypertrophy in the liver.
Mouse/CD-1	Three groups of 10 M 10F each	0, 10, & 20	Oral, gavage	6 months	< 10	≥ 10 mg/kg: Mortality; lower body weights, minimal to mild decreases in serum total protein, albumin, and globulins; decreased weights of the testes and prostate/seminal vesicles; increased severity of nephropathy in the kidneys; minimal to moderate degeneration and hypertrophy in the centrilobular region of the liver; bronchioloalveolar hyperplasia and/or adenomas, and minimal to moderate alveolar histiocytosis in the lungs; minimal to moderate skeletal muscle myopathy; and minimal to moderate seminiferous-tubular degeneration in the testes. 20 mg/kg: Mild decreases in total leukocyte and lymphocyte counts in males; and minimal to mild decreases in serum total protein, albumin, and globulins.
RAT						
Rat/SD	Four groups of 20M 20F each	0, 0.02, 0.08, & 0.3	Oral, gavage	6 months	< 0.02	≥ 0.02 mg/kg: Minimal centrilobular degeneration in the liver.
Rat/SD	Four groups of 20M 20F each	0, 0.6, 3, & 15	Oral, gavage	6 months	0.6	≥ 0.6 mg/kg: Minimal to mild decreases in serum total protein, albumin, and globulins in males; minimal to mild centrilobular degeneration in the liver (associated with enlarged hepatocellular mitochondria in males; clearly different than the hepatocellular megamitochondria reported for another antiviral

Species/Strain	N/Sex	Dose mg/kg/day	Route of Administration	Duration of Dosing	NOAEL (mg/kg)	Findings
						nucleoside analog and considered secondary to the hepatocellular degeneration); and minimal to mild skeletal-muscle myopathy. ≥ 3 mg/kg: Minimal to mild increases in serum urea nitrogen and cholesterol and minimal to moderate increases in serum AST in males. 15 mg/kg: Lower body weight in males; mild increase in total leukocyte count in males; minimal to mild increases in prothrombin time; minimal to mild increases in serum urea nitrogen, cholesterol, and sodium in females; minimal to mild increases in serum ALT and chloride; mild increases in water consumption and urine volume and a mild decrease in urine specific gravity in males; and decreased testes weight and size.
DOG						
Dog/Beagle	Four groups of 3M 3F each	0, 0.3, 3, & 30/15 (due to overt toxicity at 30 mg/kg, the high dose was reduced to 15 mg/kg on dose day 29.)	Oral, capsule	3 months	< 0.3	≥ 0.3 mg/kg: Decreased weights of the testes and prostrate; and minimal to moderate inflammation in the brain. ≥ 3 mg/kg: Decreased weights of the ovaries; minimal to mild inflammation in the spinal cord; inflammation and depletion of zymogen granules in the pancreas; degeneration of seminiferous tubules in the testes; and atrophy in the prostate. 30/15 mg/kg: Three dogs sacrificed in moribund condition after approximately 1 month of dosing. In surviving high-dose dogs: clinical signs of toxicity, clinical laboratory changes including mild to moderate decreases in RBC/WBC parameters and platelet counts; a mild increase in serum gamma glutamyl transferase; increased myeloid/erythroid ratio and a moderately reduced number of megakaryocytes in bone-marrow smears; and a moderate increase in urine specific gravity. In sacrificed and surviving dogs: myeloid/erythroid depletion in the bone marrow; and lymphoid depletion in lymph nodes.
Dog/Beagle	Control 4M 4F; 0.1 mg/kg 3M 3F; 15 mg/kg 6M 6F.	0, 0.1, & 15	Oral, capsule	3 months	0.1	0.1 mg/kg: No drug-related changes. 15 mg/kg: Changes generally were consistent with

Species/Strain	N/Sex	Dose mg/kg/day	Route of Administration	Duration of Dosing	NOAEL (mg/kg)	Findings
	2M 2 F control and 3M 3F at 15 mg/kg evaluated after 3-month postdose period.					those at 30/15 mg/kg in the initial 3-month study, but target organs were limited to CNS, pancreas, and testes; all changes were reversible or showed evidence of reversibility (testes weight).
MONKEY						
Monkey/Cynomolgus	Four groups of 6M 6F each; 2M 2F used for interim evaluation after 3 months of dosing	0, 0.4, 4, & 40	Oral, gavage	1 year	40	0.4 and 4 mg/kg: No drug-related changes. 40 mg/kg: Minimal increases in serum urea nitrogen and potassium.

Table 3 – REPRODUCTION AND TERATOLOGY

Study Type Species/Strain	N/ Sex	Dose mg/kg/day (multiple of human exposure	Duration of dosing	Route of Administration	Findings
Oral Study of Fertility and Early Embryonic Development-Treated Female Rats Rats/SD	Four groups of 25 F each	0, 0.3, 3, & 30	2 Weeks premating through Gestation Day 7	Oral, gavage	≥ 0.3 mg/kg: No drug-related changes.
Oral Study of Fertility and Early Embryonic Development-Treated Male Rats Rats/SD	Four groups of 25 M each	0, 0.1, 1, & 10	4 Weeks premating until scheduled euthanasia (33 to 42 daily doses)	Oral, gavage	0.1 and 1 mg/kg: No drug-related changes. 10 mg/kg: Decreased body weight and body-weight gain.
Oral Study of Embryo-Fetal Development in Rats Rats/SD	Four groups of 22 F each	0, 2, 20, & 200	Gestation Days 6-15	Oral, gavage	0.2 mg/kg: No drug-related changes. ≥ 20 mg/kg: In the dams: lower body weights and body-weight gains. In the fetuses: increases in embryo-fetal death (resorptions) with associated decreases in live-litter sizes. 200 mg/kg: In the dams: 1 death, decreased food consumption, and increased incidence of reduced/absent feces. In the fetuses: lower body weight; tail and vertebrae malformations; delays in ossification of the vertebrae, sternebrae and phalanges; and increases in the number of lumbar vertebrae and ribs.
Oral Study of Embryo-Fetal Development in Rabbits Rabbit/NZW	Four groups of 20 F each	0, 1, 4, & 16	Gestation Days 6-18	Oral, gavage	1 and 4 mg/kg: No drug-related changes. 16 mg/kg: In the fetuses: increases in embryo-fetal death (resorptions) with associated decreases in live-litter sizes; developmental delays in ossification of the hyoid; and an increased incidence of 13th rib.
Oral Study of Pre- and Postnatal Development in Rats Rats/SD	Four groups of 25 F each	0, 0.3, 3, & 30	Gestation Day 6 through Day 20 of Lactation	Oral, gavage	0.3 and 3 mg/kg: No drug-related changes. 30 mg/kg: In the dams: reduced body-weight gain.

Table 4 – CARCINOGENICITY

Species/Strain	N/ Sex	Dose mg/kg/day	Route of Administration	Duration of Dosing	Findings
Carcinogenicity Study in Mice Mouse/CD-1	Four groups of 60M, 60F each	0, 0, 0.004, 0.04, 0.4, & 4	Oral, gavage	24 months	0.004 mg/kg: No drug-related changes. ≥ 0.04 mg/kg: Increased incidences of bronchiolo/alveolar adenoma in the lungs in males. ≥ 0.4 mg/kg: Increased mortality; hyperplasia of alveolar epithelium, leukocytosis/interstitial inflammation, and infiltration of the alveolar spaces by alveolar macrophages in the lungs. 4 mg/kg: Lower body weights and body-weight gains; increased incidences of focal hyperplasia of bronchiolar epithelium and alveolar fibrosis in the lungs and hematocyts, thrombi and ectasia in the ovaries; and increased tumor incidences including: bronchiolo/alveolar carcinoma in the lung, bronchiolo/alveolar adenoma (females) in the lungs, hepatocellular carcinoma (males) in the liver, and vascular tumors (females).
Carcinogenicity Study in Rats Rat/SD	Six groups of 60M, 60F each	0, 0, 0.003, 0.02, & 0.2, and 1.4 (M); 0, 0, 0.01, 0.06, 0.4, & 2.6 (F)	Oral, gavage	24 months	0.003 mg/kg (males) and 0.01 and 0.06 mg/kg (females): No drug-related changes. ≥ 0.2 mg/kg (males): Increased incidences of focal hyperplasia in the acinar (exocrine) pancreas and hepatocellular alterations in the liver. 1.4 mg/kg (males): Decreased body weight; increased incidences of hepatocellular vacuolation, testicular degeneration, and chronic progressive nephropathy; and increased tumor incidences including malignant glioma in the brain. ≥0.4 mg/kg (females): Increased incidences of hepatocellular alterations. 2.6 mg/kg (females): Increased incidence of hepatocellular vacuolation; and increased tumor incidences including hepatocellular adenoma carcinoma malignant glioma in the brain, and skin fibroma.

Table 5 – MUTAGENICITY

Test/Test System	Sex	Concentration/Dose	Route of Administration	Duration of Dosing	Effects
IN VITRO					
Ames/S. typhimurium and E. Coli	NA	312.5 to 5000 ng/plate, both with and without metabolic activation	NA	48 hr	Not mutagenic
Gene Mutation/CHO cells-HGPRT locus	NA	50 to 1000 μg/mL without metabolic activation	NA	4 hr	Not mutagenic when tested to cytotoxic concentrations
Cytogenetics/Primary Human Lymphocytes	NA	2.5 to 20 μg/mL (without metabolic activation) and 2.5 to 200 μg/mL with metabolic activation	NA	24 hr without metabolic activation and 5 hr with metabolic activation	Cytotoxicity at ≥ 5 μg/mL (without metabolic activation) and at 200 μg/mL (with metabolic activation. Increased chromosome aberrations at ≥ 10 μg/mL (without metabolic activation) and at ≥ 50 μg/mL with metabolic activation.
Cell transformation/Syrian hamster embryo cells	NA	0.125 to 2.0 μg/mL	NA	7 days	No increase in morphologically transformed cells when tested to cytotoxic concentrations
IN VIVO					
Micronucleus/Rat	Male	2 to 2000 mg/kg daily	Oral, gavage	3 days	Not genotoxic
DNA Repair/Rat	Male	2 to 2000 mg/kg	Oral, gavage	Single Dose	Not genotoxic

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PART III: CONSUMER INFORMATION

PrBARACLUDE*
(entecavir)

This leaflet is Part III of a three-part "Product Monogaph" published when BARACLUDE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BARACLUDE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for
BARACLUDE is a prescription medicine used for chronic infection with hepatitis B virus (HBV) in adults who also have active liver damage.

What it does
- 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 reduce the damage to the liver by HBV

BARACLUDE will not cure HBV infection.

It is important to stay under your healthcare provider's care while taking BARACLUDE. Your healthcare provider will test the level of the hepatitis B virus in your blood regularly.

When it should not be used
Do not take BARACLUDE if you are allergic to any of its ingredients. The active ingredient in BARACLUDE is entecavir. See "What the nonmedicinal ingredients are" 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 the medicinal ingredient is:
Entecavir

What the nonmedicinal ingredients are:
BARACLUDE tablets: lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, magnesium stearate, titanium dioxide, hypromellose, polyethylene glycol 400, polysorbate 80.
BARACLUDE Oral Solution: citric acid, maltitol, methylparaben, orange flavor, propylparaben and sodium citrate.

What dosage forms it comes in:
- BARACLUDE film-coated tablets
- BARACLUDE Oral Solution

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 to 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.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Severe worsening of hepatitis (liver inflammation) has occurred in patients who have stopped taking anti-hepatitis B therapy (including BARACLUDE). Your doctor will monitor your condition in this case and may resume therapy.

Lactic acidosis (increase in acid level of blood) and severe hepatomegaly with steatosis (enlarged fatty liver), including fatal cases have been reported in patients using nucleoside analogue medicines, including BARACLUDE, either alone or in combination. Reports of lactic acidosis with BARACLUDE often involved patients who were seriously ill due to their liver disease or other medical condition. Lactic acidosis is a medical emergency and

must be treated in the hospital. Call your healthcare provider right away if you get any of the signs of lactic acidosis (see table Serious Side Effects and What to do About them).

Your hepatitis B 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.

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.

BEFORE you use BARACLUDE talk to your healthcare provider about all of your medical conditions, including if you:

- have had a liver transplant.
- have kidney problems. Your doctor may need to adjust your BARACLUDE dose or dose schedule.
- have diabetes. The oral solution contains 6.5 mg/10 mL of maltitol as a sweetener.
- 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.
- are lactose intolerant. BARACLUDE tablets contain lactose. If you have been told that you have intolerance to some sugars, contact your doctor before taking this medicine.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription 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.

INTERACTIONS WITH THIS MEDICATION

BARACLUDE may interact with other medicines that leave the body through the kidneys.

PROPER USE OF THIS MEDICATION

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.

Usual dose

The usual dose of BARACLUDE Tablets in adults and children over 16 years of age is either one or two 0.5 mg tablets once daily by mouth. The usual dose of BARACLUDE Oral Solution in adults and children over 16 years of age 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 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.
- When your supply of BARACLUDE starts to run low, get more from your healthcare provider or pharmacy. Do not run out of BARACLUDE.

Overdose

In case of drug overdosage, contact a healthcare practitioner (e.g. doctor) hospital emergency department or regional poison control centre, even if there are no symptoms.

Missed Dose

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Lactic acidosis (high level of lactic acid in the blood) **Symptoms:**			
Feeling very weak or tired		✓	
Unusual (not normal) muscle pain		✓	
Trouble breathing		✓	
Stomach pain with nausea and vomiting		✓	
Feeling cold especially in arms and legs		✓	
Feeling dizzy or lightheaded		✓	
Fast or irregular heartbeat		✓	
Worsening hepatitis (inflamed liver), liver enlargement (hepatomegaly) or fatty liver Symptoms:			
Skin or the white part of eyes turn yellow (jaundice)		✓	
Dark urine		✓	
Bowel movements (stools) turn light in colour		✓	
Nausea		✓	
Lower stomach pain		✓	
Loss of appetite for several days or longer		✓	

This is not a complete list of side effects. For any unexpected effects while taking BARACLUDE, contact your doctor or pharmacist.

HOW TO STORE IT

Store BARACLUDE Tablets or Oral Solution at room temperature, 15˚ to 30˚ C (59˚ F to 86˚ F). 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.

Discard BARACLUDE when it is outdated or no longer needed by returning the unused portion to your pharmacist for proper disposal.

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

General Information
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 also call Bristol Myers Squibb Canada at telephone number 1-866-463-6267.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reactions reporting guidelines are available on the MedEffect[tm] Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Bristol-Myers Squibb Canada at 1-866-463-6267.

This leaflet was prepared by Bristol-Myers Squibb Canada

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