

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-797**

**21-798**

**APPROVED LABELING**

**Baraclude™**

**Rx only**

**(entecavir)**

**Baraclude™ (entecavir) Tablets**

**Baraclude™ (entecavir) Oral Solution**

**Patient Information Included**

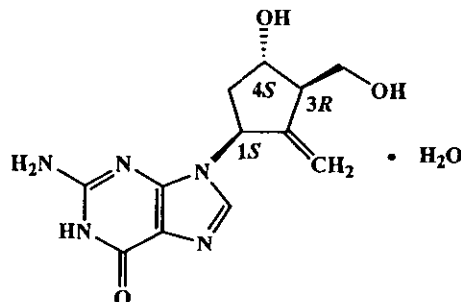
### WARNINGS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals.

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS).

### DESCRIPTION

BARACLUDGE™ is the tradename for entecavir, a guanosine nucleoside analogue with selective activity against hepatitis B virus (HBV). The chemical name for entecavir is 2-amino-1,9-dihydro-9-[(1*S*,3*R*,4*S*)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6*H*-purin-6-one, monohydrate. Its molecular formula is C<sub>12</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub>•H<sub>2</sub>O, which corresponds to a molecular weight of 295.3. Entecavir has the following structural formula:



Entecavir is a white to off-white powder. It is slightly soluble in water (2.4 mg/mL), and the pH of the saturated solution in water is 7.9 at  $25 \pm 0.5^\circ \text{C}$ .

BARACLUDE film-coated tablets are available for oral administration in strengths of 0.5 mg and 1 mg of entecavir. BARACLUDE 0.5-mg and 1-mg film-coated tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. The tablet coating contains titanium dioxide, hypromellose, polyethylene glycol 400, polysorbate 80 (0.5-mg tablet only), and iron oxide red (1-mg tablet only). BARACLUDE Oral Solution is available for oral administration as a ready-to-use solution containing 0.05 mg of entecavir per milliliter. BARACLUDE Oral Solution contains the following inactive ingredients: maltitol, sodium citrate, citric acid, methylparaben, propylparaben, and orange flavor.

## **MICROBIOLOGY**

### **Mechanism of Action**

Entecavir, a guanosine nucleoside analogue with activity against HBV polymerase, is efficiently phosphorylated to the active triphosphate form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine triphosphate, entecavir triphosphate functionally inhibits all three activities of the HBV polymerase (reverse transcriptase, rt): (1) base priming, (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand of HBV DNA. Entecavir triphosphate has an inhibition constant ( $K_i$ ) for HBV DNA polymerase of  $0.0012 \mu\text{M}$ . Entecavir triphosphate is a weak inhibitor of cellular DNA polymerases  $\alpha$ ,  $\beta$ , and  $\delta$  and mitochondrial DNA polymerase  $\gamma$  with  $K_i$  values ranging from 18 to  $>160 \mu\text{M}$ .

### **Antiviral Activity**

Entecavir inhibited HBV DNA synthesis (50% reduction,  $\text{EC}_{50}$ ) at a concentration of  $0.004 \mu\text{M}$  in human HepG2 cells transfected with wild-type HBV. The median  $\text{EC}_{50}$  value for entecavir against lamivudine-resistant HBV (rtL180M, rtM204V) was  $0.026 \mu\text{M}$  (range  $0.010$ - $0.059 \mu\text{M}$ ). In contrast, no clinically relevant activity was noted against human immunodeficiency virus (HIV) type 1 ( $\text{EC}_{50}$  value  $>10 \mu\text{M}$ ) grown in cell culture.

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 (equivalent 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.

The coadministration of HIV nucleoside reverse transcriptase inhibitors (NRTIs) with BARACLUDGE is unlikely to reduce the antiviral efficacy of BARACLUDGE 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 at >4 times the  $C_{max}$  of entecavir.

## Resistance

### *In Vitro*

In cell-based assays, 8- to 30-fold reductions in entecavir phenotypic susceptibility were observed for lamivudine-resistant strains. Further reductions (>70-fold) in entecavir phenotypic susceptibility required the presence of primary lamivudine resistance amino acid substitutions (rtL180M and/or rtM204V/I) along with additional substitutions at residues rtT184, rtS202, or rtM250, or a combination of these substitutions with or without an rtI169 substitution in the HBV polymerase.

### Clinical Studies

- *Nucleoside-naive patients:* Eighty-one percent of HBV chronically infected nucleoside-naive patients receiving entecavir 0.5 mg once daily achieved a reduction in viral load to <300 copies/mL at 48 weeks. Genotypic analysis of serum HBV DNA from nucleoside-naive HBeAg-positive (Study AI463022; n=219) or HBeAg-negative (Study AI463027; n=211) patients detected no genotypic changes in the HBV polymerase associated with phenotypic resistance to entecavir at Week 48. No genotypic or phenotypic evidence of entecavir resistance was detected in the 2 patients who experienced a confirmed virologic rebound ( $\geq 1$  log increase from nadir) in Study AI463022.

*Lamivudine-refractory patients:* Twenty-two percent of lamivudine-refractory patients with chronic HBV infection achieved HBV DNA levels <300 copies/mL at Week 48 on entecavir 1 mg once daily. Genotypic analysis of clinical samples from those patients with detectable viral DNA identified 7% (13/189) with evidence of emerging entecavir resistance-associated substitutions at rtI169, rtT184, rtS202, and/or rtM250 by Week 48 when pre-existing lamivudine resistance mutations rtL180M and/or rtM204V/I were present. Of the 13 patients with genotypic resistance, 3 experienced virologic rebound ( $\geq 1$  log increase from nadir) by Week 48, with the majority of these 13 patients experiencing virologic rebound beyond Week 48.

## **Cross-resistance**

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, entecavir had 8- to 30-fold less inhibition of replication of HBV containing lamivudine resistance mutations rtL180M and/or rtM204V/I than of wild-type virus. Recombinant HBV genomes encoding adefovir resistance-associated substitutions at either rtN236T or rtA181V remained susceptible to entecavir. HBV isolates from lamivudine-refractory patients failing entecavir therapy were susceptible *in vitro* to adefovir but retained resistance to lamivudine.

## **CLINICAL PHARMACOLOGY**

### **Pharmacokinetics**

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

#### **Absorption**

Following oral administration in healthy subjects, entecavir peak plasma concentrations occurred between 0.5 and 1.5 hours. Following multiple daily doses ranging from 0.1 to 1.0 mg,  $C_{\max}$  and area under the concentration-time curve (AUC) at steady state increased in proportion to dose. Steady state was achieved after 6 to 10 days of once-daily administration with approximately 2-fold accumulation. For a 0.5-mg oral dose,  $C_{\max}$  at steady state was 4.2 ng/mL and trough plasma concentration ( $C_{\text{trough}}$ ) was 0.3 ng/mL. For a 1-mg oral dose,  $C_{\max}$  was 8.2 ng/mL and  $C_{\text{trough}}$  was 0.5 ng/mL.

In healthy subjects, the bioavailability of the tablet was 100% relative to the oral solution. The oral solution and tablet may be used interchangeably.

*Effects of food on oral absorption:* Oral administration of 0.5 mg of entecavir with a standard high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) resulted in a delay in absorption (1.0-1.5 hour fed vs. 0.75 hours fasted), a decrease in  $C_{\max}$  of 44%-46%, and a decrease in AUC of 18%-20%. Therefore, BARACLUDGE 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.

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

## Metabolism and Elimination

Following administration of <sup>14</sup>C-entecavir in humans and rats, no oxidative or acetylated metabolites were observed. Minor amounts of phase II metabolites (glucuronide and sulfate conjugates) were observed. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

After reaching peak concentration, entecavir plasma concentrations decreased in a bi-exponential manner with a terminal elimination half-life of approximately 128-149 hours. The observed drug accumulation index is approximately 2-fold with once-daily dosing, suggesting an effective accumulation half-life of approximately 24 hours.

Entecavir is predominantly eliminated by the kidney with urinary recovery of unchanged drug at steady state ranging from 62% to 73% of the administered dose. Renal clearance is independent of dose and ranges from 360 to 471 mL/min suggesting that entecavir undergoes both glomerular filtration and net tubular secretion (see **PRECAUTIONS: Drug Interactions**).

## Special Populations

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

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

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

*Pediatrics:* Pharmacokinetic studies have not been conducted in children.

*Renal impairment:* 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 1.

**Table 1: Pharmacokinetic Parameters in Subjects with Selected Degrees of Renal Function**

	Renal Function Group					
	Baseline Creatinine Clearance (mL/min)				Severe Managed with Hemodialysis <sup>a</sup>	Severe Managed with CAPD
	Unimpaired >80 (n=6)	Mild >50-≤80 (n=6)	Moderate 30-50 (n=6)	Severe <30 (n=6)		
C <sub>max</sub> (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 <sub>(0-7)</sub> (ng•hr/mL) (CV)	27.9 (25.6)	51.5 (22.8)	69.5 (22.7)	145.7 (31.5)	233.9 (28.4)	221.8 (11.6)
CLR (mL/min) (SD)	383.2 (101.8)	197.9 (78.1)	135.6 (31.6)	40.3 (10.1)	NA	NA
CLT/F (mL/min) (SD)	588.1 (153.7)	309.2 (62.6)	226.3 (60.1)	100.6 (29.1)	50.6 (16.5)	35.7 (19.6)

<sup>a</sup> 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 entecavir administered 2 hours before the hemodialysis session, hemodialysis removed approximately 13% of the entecavir dose over 4 hours. CAPD removed approximately 0.3% of the dose over 7 days. Entecavir should be administered after hemodialysis.

**Hepatic impairment:** The pharmacokinetics of entecavir following a single 1-mg dose were studied in patients (without chronic hepatitis B infection) with moderate or severe hepatic impairment (Child-Pugh Class B or C). The pharmacokinetics of entecavir were similar between hepatically impaired patients and healthy control subjects; therefore, no dosage adjustment of BARACLUDE is recommended for patients with hepatic impairment.

**Post-liver transplant:** The safety and efficacy of BARACLUDE in liver transplant recipients are unknown. However, in a small pilot study of entecavir use in HBV-infected liver transplant recipients on a stable dose of cyclosporine A (n=5) or tacrolimus (n=4), entecavir exposure was approximately 2-fold the exposure in healthy subjects with normal renal function. Altered renal function contributed to the increase in entecavir exposure in these 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.**)

### **Drug Interactions (see also PRECAUTIONS: Drug Interactions)**

The metabolism of entecavir was evaluated in *in vitro* and *in vivo* studies. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system. At concentrations up to approximately 10,000-fold higher than those obtained in humans, entecavir inhibited none of the major human CYP450 enzymes 1A2, 2C9, 2C19, 2D6, 3A4, 2B6, and 2E1. At concentrations up to approximately 340-fold higher than those observed in humans, entecavir did not induce the human CYP450 enzymes 1A2, 2C9, 2C19, 3A4, 3A5, and 2B6. (See **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 entecavir.

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

### **INDICATIONS AND USAGE**

BARACLUE (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 histologic, virologic, biochemical, and serologic responses after one year of treatment in nucleoside-treatment-naïve and lamivudine-resistant 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.

### **Description of Clinical Studies**

The safety and efficacy of BARACLUE were evaluated in three Phase 3 active-controlled trials. 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). Patients had persistently elevated ALT levels  $\geq 1.3$  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 BARACLUE were also evaluated in a study of 68 patients co-infected with HBV and HIV.



### **Nucleoside-Naive Patients With Compensated Liver Disease**

*HBeAg-positive:* Study AI463022 was a multinational, randomized, double-blind study of BARACLUDE 0.5 mg once daily versus lamivudine 100 mg once daily for 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- $\alpha$ . At baseline, patients had a mean Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA as measured by Roche COBAS Amplicor<sup>®</sup> PCR assay was 9.66 log<sub>10</sub> 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 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- $\alpha$ . 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<sub>10</sub> 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  $\geq 2$ -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 2. Selected virologic, biochemical, and serologic outcome measures are shown in Table 3

**Table 2: 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)	
	BARACLUDGE 0.5 mg n=314 <sup>a</sup>	Lamivudine 100 mg n=314 <sup>a</sup>	BARACLUDGE 0.5 mg n=296 <sup>a</sup>	Lamivudine 100 mg n=287 <sup>a</sup>
<b>Histologic Improvement (Knodell Scores)</b>				
Improvement <sup>b</sup>	72%*	62%	70%*	61%
No improvement	21%	24%	19%	26%
<b>Ishak Fibrosis Score</b>				
Improvement <sup>c</sup>	39%	35%	36%	38%
No change	46%	40%	41%	34%
Worsening <sup>c</sup>	8%	10%	12%	15%
Missing Week 48 biopsy	7%	14%	10%	13%

<sup>a</sup> Patients with evaluable baseline histology (baseline Knodell Necroinflammatory Score  $\geq 2$ ).

<sup>b</sup>  $\geq 2$ -point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.

<sup>c</sup> For Ishak Fibrosis Score, improvement =  $\geq 1$ -point decrease from baseline and worsening =  $\geq 1$ -point increase from baseline.

\* p<0.05

**Table 3: 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)	
	BARACLUDGE 0.5 mg n=354	Lamivudine 100 mg n=355	BARACLUDGE 0.5 mg n=325	Lamivudine 100 mg n=313
	HBV DNA <sup>a</sup>			
Proportion undetectable (<300 copies/mL)	67%*	36%	90%*	72%
Mean change from baseline (log <sub>10</sub> copies/mL)	-6.86*	-5.39	-5.04*	-4.53
ALT normalization (≤1 X ULN)	68%*	60%	78%*	71%
HBeAg seroconversion	21%	18%	N/A	N/A

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

\* p<0.05

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

### Lamivudine-Refractory Patients

Study AI463026 was a multinational, randomized, double-blind study of BARACLUDGE in 286 (of 293 randomized) patients with lamivudine-refractory chronic hepatitis B infection. Patients receiving lamivudine at study entry either switched to BARACLUDGE 1 mg once daily (with neither a washout nor an overlap period) or continued on lamivudine 100 mg for 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- $\alpha$ . 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<sub>10</sub> copies/mL, and mean serum ALT level was 128 U/L. Paired, adequate liver biopsy samples were available for 87% of patients.

BARACLUDGE was superior to lamivudine on the coprimary endpoint of Histologic Improvement (using the Knodell Score at Week 48). These results and change in Ishak Fibrosis Score are shown in Table 4. Table 5 shows selected virologic, biochemical, and serologic endpoints.

**Table 4: Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Lamivudine-Refractory Patients in Study AI463026**

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

<sup>a</sup> Patients with evaluable baseline histology (baseline Knodell Necroinflammatory Score  $\geq 2$ ).

<sup>b</sup>  $\geq 2$ -point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.

<sup>c</sup> For Ishak Fibrosis Score, improvement =  $\geq 1$ -point decrease from baseline and worsening =  $\geq 1$ -point increase from baseline.

\*  $p < 0.01$

**Table 5: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Lamivudine-Refractory Patients in Study AI463026**

	BARACLUDGE 1 mg n=141	Lamivudine 100 mg n=145
<b>HBV DNA<sup>a</sup></b>		
Proportion undetectable ( $< 300$ copies/mL)	19%*	1%
Mean change from baseline ( $\log_{10}$ copies/mL)	-5.11*	-0.48
ALT normalization ( $\leq 1 \times$ ULN)	61%*	15%
HBeAg seroconversion	8%	3%

<sup>a</sup> Roche COBAS AmpliCor PCR assay (LLOQ = 300 copies/mL).

\*  $p < 0.0001$

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

### **Post-Treatment Follow-up**

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 normalization ( $<1.25$  X ULN, in HBeAg-negative patients) at Week 48. For the 21% of nucleoside-naive, HBeAg-positive BARACLUDE-treated patients who met response criteria, response was sustained throughout the 24-week post-treatment follow-up period in 82%. For the 85% of nucleoside-naive, HBeAg-negative BARACLUDE-treated patients who met response criteria, response was sustained throughout the 24-week post-treatment follow-up period in 48%. Few lamivudine-refractory patients met the response criteria and were eligible to discontinue treatment. These protocol-specified patient management guidelines are not intended as guidance for clinical practice.

### **Special Populations**

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 Table 6. There are no data in patients with HIV/HBV co-infection who have not received prior lamivudine therapy.

**Table 6: Virologic and Biochemical Endpoints at Week 24, Study AI463038**

	BARACLUDGE 1 mg <sup>a</sup> n=51	Placebo <sup>a</sup> n=17
HBV DNA <sup>b</sup>		
Proportion undetectable (<300 copies/mL)	6%	0
Mean change from baseline (log <sub>10</sub> copies/mL)	-3.65 <sup>*</sup>	+0.11
ALT normalization (≤1 X ULN)	34%	8%

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

<sup>b</sup> Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).

<sup>\*</sup> p<0.0001

## CONTRAINDICATIONS

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

## WARNINGS

### Exacerbations of Hepatitis After Discontinuation of Treatment

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see **ADVERSE REACTIONS: Exacerbations of Hepatitis After Discontinuation of Treatment**).

## PRECAUTIONS

### General

### Renal Impairment

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

### **Liver Transplant Recipients**

The safety and efficacy of BARACLUDE in liver transplant recipients are unknown. If BARACLUDE treatment is determined to be necessary for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus, renal function must be carefully monitored both before and during treatment with BARACLUDE (see **CLINICAL PHARMACOLOGY: Special Populations** and **DOSAGE AND ADMINISTRATION: Renal Impairment**).

### **Information for Patients**

A patient package insert (PPI) for BARACLUDE is available for patient information.

Patients should remain under the care of a physician while taking BARACLUDE. They should discuss any new symptoms or concurrent medications with their physician.

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

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

Patients should be advised that treatment with BARACLUDE has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination (see **PRECAUTIONS: Labor and Delivery**).

### **Drug Interactions**

Since entecavir is primarily eliminated by the kidneys (see **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. Coadministration of entecavir with lamivudine, adefovir dipivoxil, or tenofovir disoproxil fumarate did not result in significant drug interactions. The effects of coadministration of BARACLUDE with other drugs that are renally eliminated or are known to affect renal function have not been evaluated, and patients should be monitored closely for adverse events when BARACLUDE is coadministered with such drugs.

## **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

In mice, lung adenomas were increased in males and females at exposures 3 and 40 times those in humans. Lung carcinomas in both male and female mice were increased at exposures 40 times those in humans. Combined lung adenomas and carcinomas were increased in male mice at exposures 3 times and in female mice at exposures 40 times those in humans. Tumor development was preceded by pneumocyte proliferation in the lung, which was not observed in rats, dogs, or monkeys administered entecavir, supporting the conclusion that lung tumors in mice may be a species-specific event. Hepatocellular carcinomas were increased in males and combined liver adenomas and carcinomas were also increased at exposures 42 times those in humans. Vascular tumors in female mice (hemangiomas of ovaries and uterus and hemangiosarcomas of spleen) were increased at exposures 40 times those in humans. In rats, hepatocellular adenomas were increased in females at exposures 24 times those in humans; combined adenomas and carcinomas were also increased in females at exposures 24 times those in humans. Brain gliomas were induced in both males and females at exposures 35 and 24 times those in humans. Skin fibromas were induced in females at exposures 4 times those in humans.

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

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



## **Pregnancy**

### **Pregnancy Category C**

Reproduction studies have been performed in rats and rabbits at orally administered doses of 200 and 16 mg/kg/day and showed no embryotoxicity or maternal toxicity in rat and rabbit at doses producing systemic exposures approximately 28 and 212 times those achieved at the highest recommended dose of 1 mg/day in humans. In rats, maternal toxicity, embryo-fetal toxicity (resorptions), lower fetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternbrae, and phalanges), and extra lumbar vertebrae and ribs were observed at exposures 3100 times those in humans. In rabbits, embryo-fetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed at exposures 883 times those in humans. In a peri-post-natal study, no adverse effects on offspring were seen with entecavir administered orally to rats at exposures >94 times those in humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BARACLUE should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits.

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

### **Labor and Delivery**

There are no studies in pregnant women and no data on the effect of BARACLUE on transmission of HBV from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV.

### **Nursing Mothers**

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 BARACLUE.

### **Pediatric Use**

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

## **Geriatric Use**

Clinical studies of BARACLUDE did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Entecavir is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **DOSAGE AND ADMINISTRATION: 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**

Assessment of adverse reactions is based on four 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 107 weeks. Median duration of therapy was 54 weeks for BARACLUDE-treated patients and 53 weeks for lamivudine-treated patients in Studies AI463022 and AI463027 and 69 weeks for BARACLUDE-treated patients and 52 weeks for lamivudine-treated patients in Studies AI463026 and AI463014. The safety profiles of BARACLUDE and lamivudine were comparable in these studies. The safety profile of BARACLUDE 1 mg (n=51) in HIV/HBV co-infected 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.

The most common 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. Also see **WARNINGS** and **PRECAUTIONS**.

## Clinical Adverse Events

Selected clinical adverse events of moderate-severe intensity and considered at least possibly related to treatment occurring during therapy in four clinical studies in which BARACLUDGE was compared with lamivudine are presented in Table 7.

**Table 7: Selected Clinical Adverse Events<sup>a</sup> of Moderate-Severe Intensity (Grades 2-4) Reported in Four Entecavir Clinical Trials**

Body System/ Adverse Event	Nucleoside-Naive <sup>b</sup>		Lamivudine-Refractory <sup>c</sup>	
	BARACLUDGE 0.5 mg n=679	Lamivudine 100 mg n=668	BARACLUDGE 1 mg n=183	Lamivudine 100 mg n=190
<b>Gastrointestinal</b>				
Diarrhea	<1%	0	1%	0
Dyspepsia	<1%	<1%	1%	0
Nausea	<1%	<1%	<1%	2%
Vomiting	<1%	<1%	<1%	0
<b>General</b>				
Fatigue	1%	1%	3%	3%
<b>Nervous System</b>				
Headache	2%	2%	4%	1%
Dizziness	<1%	<1%	0	1%
Somnolence	<1%	<1%	0	0
<b>Psychiatric</b>				
Insomnia	<1%	<1%	0	<1%

<sup>a</sup> Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

<sup>b</sup> Studies AI463022 and AI463027.

<sup>c</sup> Includes Study AI463026 and the BARACLUDGE 1-mg and lamivudine treatment arms of Study AI463014, a Phase 2 multinational, randomized, double-blind study of three doses of BARACLUDGE (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.

## Laboratory Abnormalities

Frequencies of selected treatment-emergent laboratory abnormalities reported during therapy in four clinical trials of BARACLUDGE compared with lamivudine are listed in Table 8.

**Table 8: Selected Treatment-Emergent<sup>a</sup> Laboratory Abnormalities Reported in Four Entecavir Clinical Trials**

Test	Nucleoside-Naive <sup>b</sup>		Lamivudine-Refractory <sup>c</sup>	
	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 X ULN	11%	16%	12%	24%
AST >5.0 X ULN	5%	8%	5%	17%
Albumin <2.5 g/dL	<1%	<1%	0	2%
Total bilirubin >2.5 g/dL	2%	2%	3%	2%
Amylase >2.0 X ULN	2%	2%	3%	3%
Lipase >2.0 X ULN	7%	6%	8%	7%
Creatinine >3.0 X ULN	0	0	0	0
Confirmed creatinine increase ≥0.5 mg/dL	1%	1%	2%	1%
Hyperglycemia, fasting >250 mg/dL	2%	1%	2%	1%
Glycosuria <sup>d</sup>	4%	3%	4%	6%
Hematuria <sup>d</sup>	9%	10%	9%	6%
Platelets <50,000/mm <sup>3</sup>	<1%	<1%	<1%	<1%

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

<sup>b</sup> Studies AI463022 and AI463027.

<sup>c</sup> 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.

<sup>d</sup> Grade 3 = 3+, large (also 500, 1000, >1000 and ≥1000 for glycosuria); grade 4 = 4+, 5+, marked, severe (also +++++, 4+:MANY for hematuria).

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<sub>10</sub>/mL reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

### Exacerbations of Hepatitis After Discontinuation of Treatment (see also WARNINGS)

In the Phase 3 studies, a subset of patients was allowed to discontinue treatment at 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 baseline level. As demonstrated in Table 9, a

proportion of patients in the nucleoside-naïve studies experienced post-treatment ALT flares. The number of lamivudine-refractory patients eligible to discontinue treatment was small, and rates of post-treatment flares in this population could not be determined. If BARACLUE is discontinued without regard to treatment response, the rate of post-treatment flares could be higher.

**Table 9: Exacerbations of Hepatitis During Off-Treatment Follow-up, Nucleoside-Naïve Patients in Studies AI463022 and AI463027**

	Patients with ALT Elevations >10 X ULN and >2 X Baseline	
	BARACLUE	Lamivudine
Nucleoside-naïve	25/431 (6%)	38/392 (10%)
HBsAg-positive <sup>a</sup>	2/134 (1%)	9/129 (7%)
HBsAg-negative <sup>b</sup>	23/297 (8%)	29/263 (11%)

<sup>a</sup> Median time to off-treatment exacerbation was 23 weeks for BARACLUE-treated patients and 12 weeks for lamivudine-treated patients.

<sup>b</sup> Median time to off-treatment exacerbation was 24 weeks for BARACLUE-treated patients and 9 weeks for lamivudine-treated patients.

## OVERDOSAGE

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

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

## DOSAGE AND ADMINISTRATION

### Recommended Dosage

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

The recommended dose of BARACLUE in adults and adolescents ( $\geq 16$  years of age) with a history of hepatitis B viremia while receiving lamivudine or known lamivudine resistance mutations is 1 mg once daily.

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

BARACLUDGE 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 (see **CLINICAL PHARMACOLOGY: Special Populations**). Dosage adjustment is recommended for patients with creatinine clearance <50 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in Table 10.

**Table 10: Recommended Dosage of BARACLUDGE 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	0.5 mg once daily
10 to <30	0.15 mg once daily	0.3 mg once daily
<10 Hemodialysis* or CAPD	0.05 mg once daily	0.1 mg once daily

\*Administer after hemodialysis.

## Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

## Duration of Therapy

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

## HOW SUPPLIED

BARACLUDGE™ (entecavir) Tablets and Oral Solution are available in the following strengths and configurations of plastic bottles with child-resistant closures:

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

BARACLUDGE 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.

### Storage

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

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

Bristol-Myers Squibb Company  
Princeton, NJ 08543 USA

Issued \_\_\_\_\_

## Patient Information

Rx only

# Baraclude™ (BEAR ah klude)

(generic name = entecavir)

## Tablets and Oral Solution

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

### What is the most important information I should know about BARACLUDGE?

**1. Some people who have taken medicines like BARACLUDGE (a nucleoside analogue) have developed a serious condition called lactic acidosis (buildup of an acid in the blood). 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 following signs of lactic acidosis.**

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

**2. Some people who have taken medicines like BARACLUDGE have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Call your healthcare provider right away if you get any of the following signs of liver problems.**

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

**3. Your hepatitis B infection may get worse or become very serious if you stop BARACLUDGE.**

- Take BARACLUDGE 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.

## **What is BARACLUDE?**

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

- BARACLUDE will not cure HBV.
- BARACLUDE may lower the amount of HBV in the body.
- BARACLUDE may lower the ability of HBV to multiply and infect new liver cells.
- BARACLUDE may improve the condition of your liver.

It is 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.

## **Does BARACLUDE lower the risk of passing HBV to others?**

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

## **Who should not take BARACLUDE?**

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

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

## What should I tell my healthcare provider before I take BARACLUDGE?

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

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

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

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

## How should I take BARACLUDGE?

- Take BARACLUDGE exactly as prescribed. Your healthcare provider will tell you how much BARACLUDGE to take. Your dose will depend on whether you have been treated for HBV infection before and what medicine you took. The usual dose of BARACLUDGE Tablets is either 0.5 mg (one white tablet) or 1 mg (one pink tablet) once daily by mouth. The usual dose of BARACLUDGE Oral Solution is either 10 mL or 20 mL once daily by mouth. Your dose may be lower if you have kidney problems.
- **Take BARACLUDGE 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 BARACLUDGE, try to take it at the same time each day.
- If you are taking BARACLUDGE 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 BARACLUDGE without talking to your healthcare provider. Your hepatitis B symptoms may get worse or become very serious if you stop taking BARACLUDGE. After you stop taking BARACLUDGE, it is important to stay under your healthcare provider's care. Your healthcare provider will need to do regular blood tests to check your liver.
- **If you forget to take BARACLUDGE**, take it as soon as you remember and then take your next dose at its regular time. If it is almost time for your next dose, skip the missed dose. Do not take two doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do.
- When your supply of BARACLUDGE starts to run low, get more from your healthcare provider or pharmacy. **Do not run out of BARACLUDGE.**
- **If you take more than the prescribed dose of BARACLUDGE**, call your healthcare provider right away.
- **What are the possible side effects of BARACLUDGE?**

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

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

The most common side effects of BARACLUDGE are headache, tiredness, dizziness, and nausea. 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.

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

### **How should I store BARACLUDGE?**

- Store BARACLUDGE Tablets or Oral Solution at room temperature, 59° to 86° F (15° to 30° C). They do not require refrigeration. Do not store BARACLUDGE 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.
- Throw away BARACLUDE when it is outdated or no longer needed by flushing tablets down the toilet or pouring the oral solution down the sink.
- **Keep BARACLUDE and all medicines out of the reach of children and pets.**

**General information about BARACLUDE:** Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use BARACLUDE for a condition for which it was not prescribed. Do not give BARACLUDE to other people, even if they have the same symptoms you have. It may harm them. This leaflet summarizes the most important information about BARACLUDE. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BARACLUDE that is written for healthcare professionals. You can also call 1-800-321-1335 or visit the BARACLUDE website at [www.Baraclude.com](http://www.Baraclude.com).

## **What are the ingredients in BARACLUDE?**

**Active Ingredient:** entecavir

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

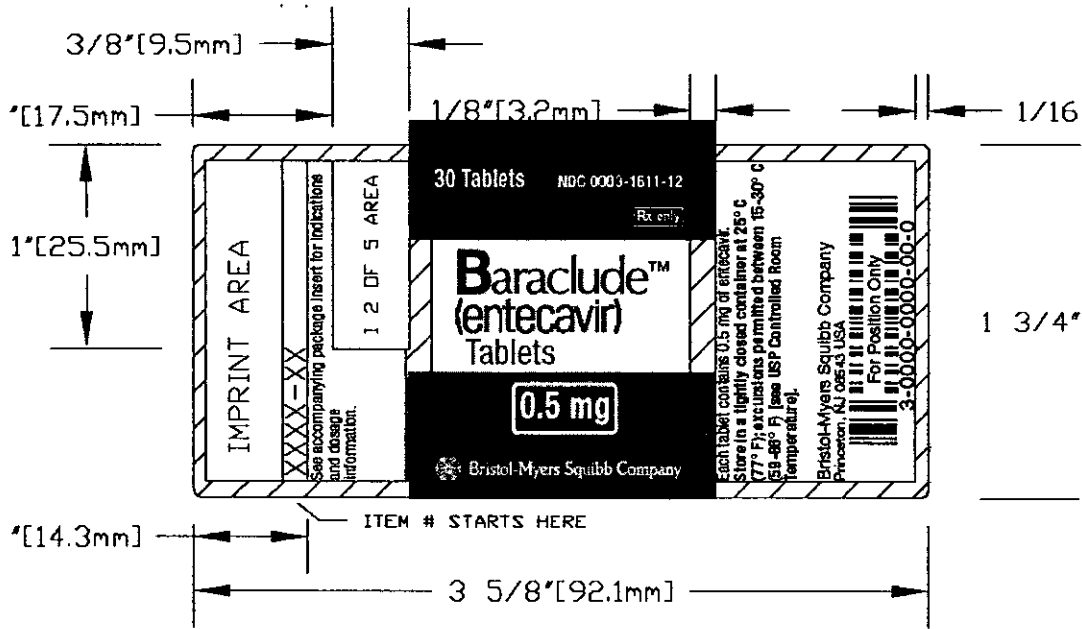
**Inactive Ingredients in BARACLUDE Oral Solution:** maltitol, sodium citrate, citric acid, methylparaben, propylparaben, and orange flavor.

Bristol-Myers Squibb Company  
Princeton, NJ 08543 USA

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

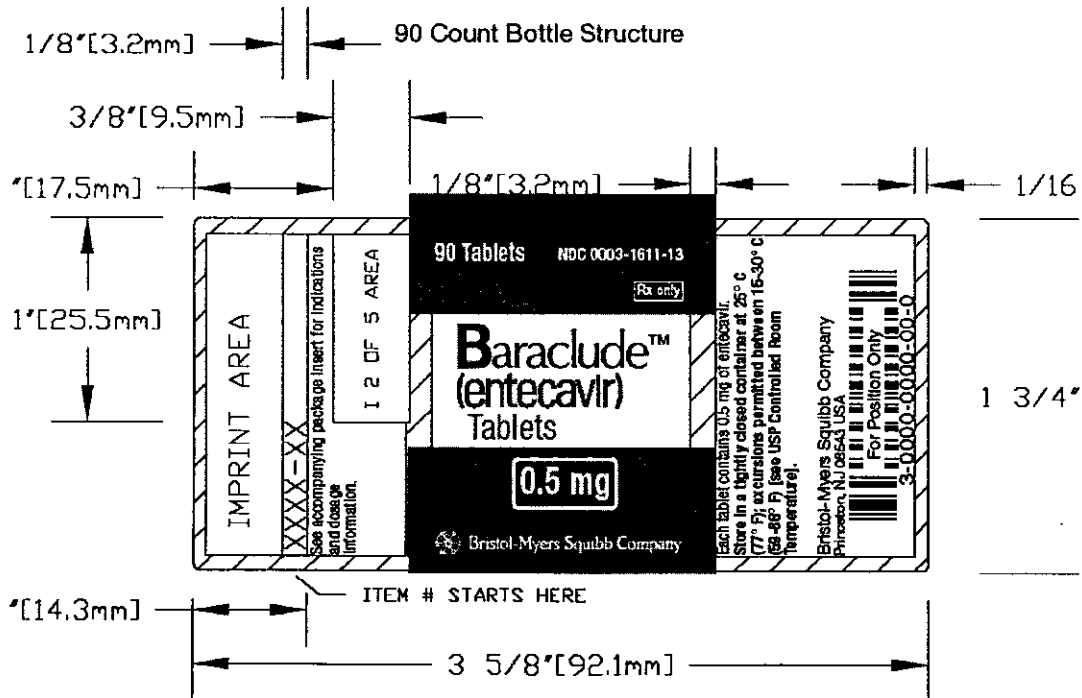
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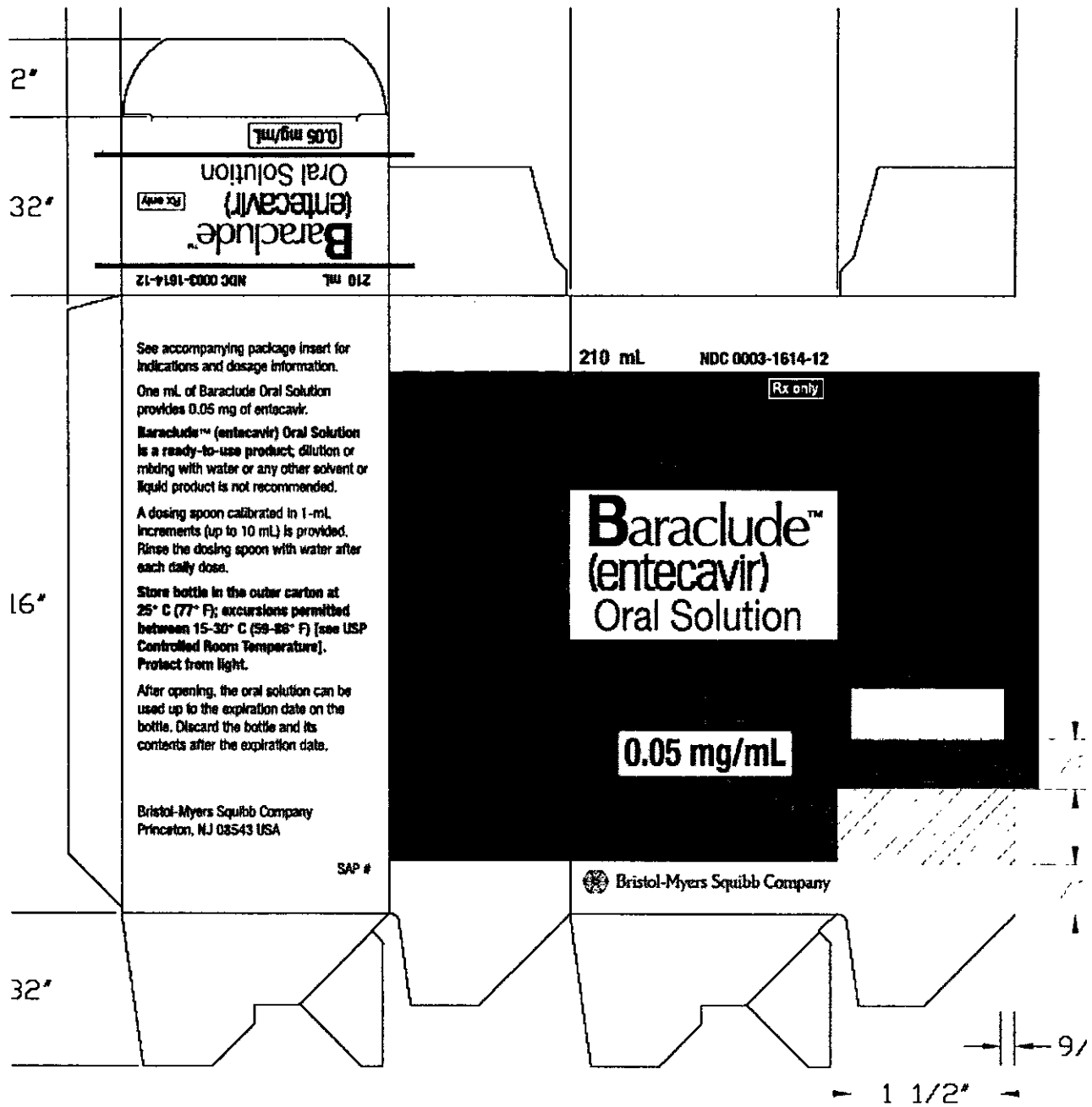


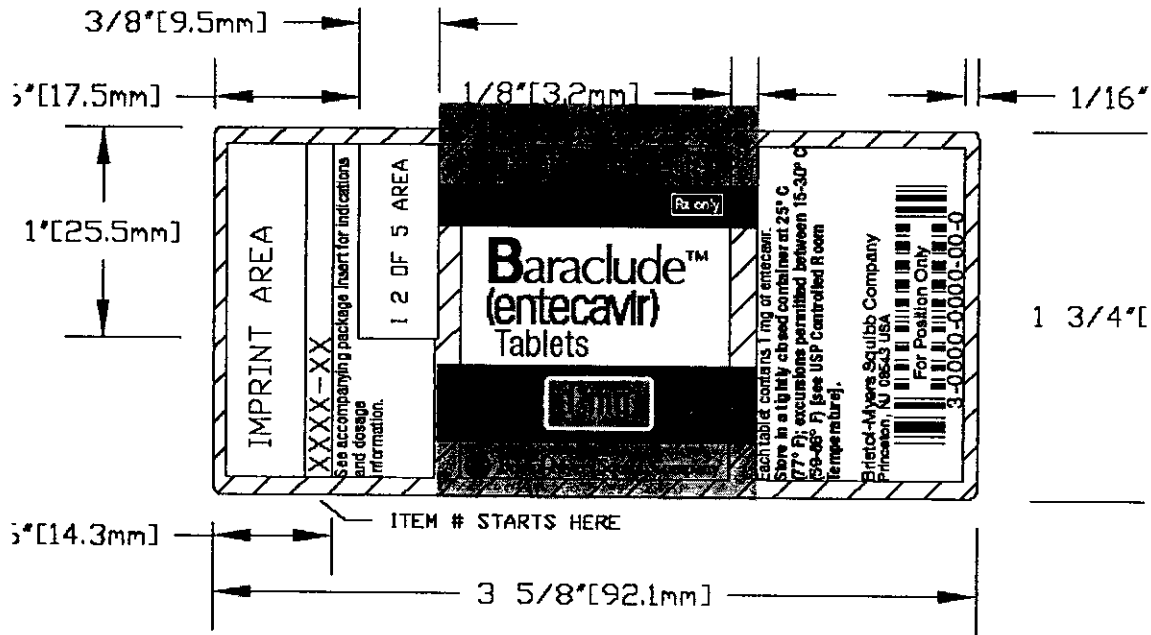
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NOTE





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90 Count Bottle Structure

