Baraclude adalah obat baru yang terdaftar tahun 2006.
Informasi di bawah ini merupakan informasi update tahun 2009.

Bristol-Myers Squibb

Baraclude*
(entecavir)

Baraclude* (entecavir) Tablets

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.

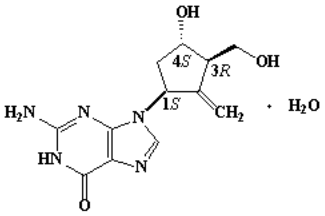
Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis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

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: Co-infection with HIV.

*** TRADEMARK**

DESCRIPTION

BARACLUDE* (entecavir) 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-[(*1S,3R,4S*)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6*H*-purin-6-one, monohydrate. Its molecular formula is $C_{12}H_{15}N_5O_3 \cdot H_2O$, which corresponds to a molecular weight of 295.3. Entecavir has the following structural formula:



Entecavir is a white to off-white powder. It is slightly soluble in water (2.4 mg/mL), and the pH of the saturated solution in water is 7.9 at 25° ± 0.5° C. BARACLUDE film-coated tablets are available for oral administration in strengths of 0.5 mg and 1 mg of entecavir. BARACLUDE 0.5-mg and 1-mg film-coated tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. The tablet coating contains titanium dioxide, hypromellose, polyethylene glycol 400, polysorbate 80 (0.5-mg tablet only), and iron oxide red (1-mg tablet only).

MICROBIOLOGY

Mechanism of Action

Entecavir, a guanosine nucleoside analogue with activity against HBV polymerase, is efficiently phosphorylated to the active triphosphate form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine triphosphate, entecavir triphosphate functionally inhibits all three activities of the HBV polymerase (reverse transcriptase, rt): (1) base priming, (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand of HBV DNA. Entecavir triphosphate is a weak inhibitor of cellular DNA polymerases α, 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).

The coadministration of HIV nucleoside reverse transcriptase inhibitors (NRTIs) with BARACLUDE is unlikely to reduce the antiviral efficacy of BARACLUDE against HBV or of any of these agents against HIV. In HBV combination assays in cell culture, abacavir, didanosine, lamivudine, stavudine, tenofovir, or zidovudine were not antagonistic to the anti-HBV activity of entecavir over a wide range of concentrations. In HIV antiviral assays, entecavir was not antagonistic to the cell culture anti-HIV activity of these six NRTIs at >4 times the C_{max} of entecavir.

Antiviral Activity against HIV

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

Resistance

In Cell Culture

In cell-based assays, 8- to 30-fold reductions in entecavir phenotypic susceptibility were observed for lamivudine-resistant strains. Further reductions (>70-fold) in entecavir phenotypic susceptibility required the presence of amino acid substitutions rtM204I/V and/or rtL180M along with additional substitutions at residues rtT184, rtS202, or rtM250, or a combination of these substitutions with or without an rtI169 substitution in the HBV polymerase.

Clinical Studies

All patients in clinical trials initially treated with entecavir 0.5 mg (nucleoside-naive, studies AI463022, AI463027, and rollover study AI463901) or 1.0 mg (lamivudine-refractory, studies AI463026, AI463014, AI463015, and rollover study AI463901) and with an on-therapy PCR HBV DNA measurement at or after Week 24 were monitored for resistance.

- *Nucleoside-naive subjects:* Genotypic evidence of entecavir resistance-associated (ETVr) substitutions at rtT184, rtS202, and/or rtM250 were identified in < 1% of patients treated with entecavir for up to 144 weeks in nucleoside-naive studies (see Table 1). These substitutions were observed only in the presence of lamivudine resistance-associated (LVDr) substitutions (rtM204V and rtL180M).

Table 1: Emerging Genotypic Entecavir Resistance Through Week 144, Nucleoside-Naive Studies

	Year 1	Year 2	Year 3[a]
Patients treated and monitored for resistance[b]	663	278	149
Emerging genotypic ETVr[c]	1 (<1%)	1 (<1%)	1 (<1%)
Cumulative probability of emerging genotypic ETVr[c]	0.2%	0.5%	1.2%
Virologic rebound[d] due to emerging ETVr[c]	1 (<1%)	0	1 (<1%)

a Results in Year 3 reflect use of a 1-mg dose of entecavir for 147 of 149 patients and of combination entecavir-lamivudine therapy for a median of 20 weeks (followed by long-term entecavir therapy) for 130 of 149 patients in a rollover study.

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

c Patients also have LVDr substitutions.

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

- *Lamivudine-refractory subjects:* ETVr substitutions were observed at baseline in isolates from 10/187 (5%) lamivudine-refractory patients treated with entecavir and monitored for resistance, indicating that prior lamivudine treatment can select these resistance substitutions and that they can exist at a low frequency before entecavir treatment. Through Week 144, 3 of the 10 patients experienced virologic rebound (≥ 1 $\log_{10}$ increase above nadir). Emerging entecavir resistance in lamivudine-refractory studies through Week 144 is summarized in Table 2.

Table 2: Emerging Genotypic Entecavir Resistance Through Week 144, Lamivudine-Refractory Studies

	Year 1	Year 2	Year 3[a]
Patients treated and monitored for resistance[b]	187	146	80
Emerging genotypic ETVr[c]	11 (6%)	12 (8%)	15 (19%)
Cumulative probability of emerging genotypic ETVr[c]	6%	15%	35%
Virologic rebound[d] due to emerging ETVr[c]	2 (1%)[e]	14 (10%)[e]	13 (16%)[e]

a Results in Year 3 reflect use of combination entecavir-lamivudine therapy for a median of 13 weeks (followed by long-term entecavir therapy) for 48 of 80 patients in a rollover study.

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

c Patients also have LVDr substitutions.

d ³1 $\log_{10}$ increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point.

e ETVr emerging in any year; rebound in specified year.

Cross-resistance

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, entecavir had 8- to 30-fold less inhibition of HBV DNA synthesis for HBV containing lamivudine and telbivudine resistance substitutions rtM204I/V ± rtL180M than for wild-type HBV. Substitutions rtM204I/V ± rtL180M, rtL80I/V, or rtV173L, which are associated with lamivudine and telbivudine resistance, also confer decreased phenotypic susceptibility to entecavir. Recombinant HBV genomes encoding adefovir resistance-associated substitutions at either rtN236T or rtA181V had 0.3- and 1.1-fold shifts in susceptibility to entecavir in cell culture, respectively. The efficacy of entecavir against HBV harboring adefovir resistance-associated substitutions has not been established in clinical trials. HBV isolates from lamivudine-refractory subjects failing entecavir therapy were susceptible in cell culture to adefovir but remained resistant to lamivudine.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The single- and multiple-dose pharmacokinetics of entecavir were evaluated in healthy subjects and subjects 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_{trough}) was 0.3 ng/mL. For a 1-mg oral dose, C_{max} was 8.2 ng/mL and C_{trough} was 0.5 ng/mL.

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

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

Distribution

Based on the pharmacokinetic profile of entecavir after oral dosing, the estimated apparent volume of distribution is in excess of total body water, suggesting that entecavir is extensively distributed into tissues.

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

Metabolism and Elimination

Following administration of ^{14}C-entecavir in humans and rats, no oxidative or acetylated metabolites were observed. Minor amounts of phase II metabolites (glucuronide and sulfate conjugates) were observed. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system (see **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 subjects (without chronic hepatitis B infection) with selected degrees of renal impairment, including subjects whose renal impairment was managed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Results are shown in Table 3.

Table 3 : Pharmacokinetic Parameters in Subjects with Selected Degrees of Renal Function

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

[a] Dosed immediately following hemodialysis.

CLR = renal clearance; CLT/F = apparent oral clearance.

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 subjects (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

subjects and healthy control subjects; therefore, no dosage adjustment of BARACLUDE is recommended for patients with hepatic impairment.

Post-liver transplant: The safety and efficacy of BARACLUDE in liver transplant recipients are unknown. However, in a small pilot study of entecavir use in HBV-infected liver transplant recipients on a stable dose of cyclosporine A (n=5) or tacrolimus (n=4), entecavir exposure was approximately 2-fold the exposure in healthy subjects with normal renal function. Altered renal function contributed to the increase in entecavir exposure in these subjects. The potential for pharmacokinetic interactions between entecavir and cyclosporine A or tacrolimus was not formally evaluated. 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
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 histologic, virologic, biochemical, and serologic responses in nucleoside-treatment-naive and lamivudine-resistant adult subjects with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease and on more limited data in adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy.

Description of Clinical Studies
Outcomes at 48 Weeks
The safety and efficacy of BARACLUDE were evaluated in three Phase 3 active-controlled trials. These studies included 1633 subjects 16 years of age or older with chronic hepatitis B 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 ³1.3 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 subjects co-infected with HBV and HIV.

Nucleoside-naive subjects with compensated liver
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 subjects with chronic hepatitis B infection and detectable HBeAg. The mean age of subjects was 35 years, 75% were male, 57% were Asian, 40% were Caucasian, and 13% had previously received interferon-a. At baseline, subjects had a mean Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA as measured by Roche COBAS Amplicor® PCR assay was 9.66 $\log_{10}$ copies/mL, and mean serum ALT level was 143 U/L. Paired, adequate liver biopsy samples were available for 89% of subjects .

HBeAg-negative (anti-HBe positive/HBV DNA positive): **Study AI463027** was a multinational, randomized, double-blind study of BARACLUDE 0.5 mg once daily versus lamivudine 100 mg once daily for a minimum of 52 weeks in 638 (of 648 randomized) nucleoside-naive subjects with HBeAg-negative (HBeAb-positive) chronic hepatitis B infection. The mean age of subjects was 44 years, 76% were male, 39% were Asian, 58% were Caucasian, and 13% had previously received interferon-a. At baseline, subjects had a mean Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA as measured by Roche COBAS Amplicor PCR assay was 7.58 $\log_{10}$ copies/mL, and mean serum ALT level was 142 U/L. Paired, adequate liver biopsy samples were available for 88% of subjects.

In Studies AI463022 and AI463027, BARACLUDE was superior to lamivudine on the primary efficacy endpoint of Histologic Improvement, defined as ³2-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 4. Selected virologic, biochemical, and serologic outcome measures are shown in Table 5.

Table 4 : Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Nucleoside-Naive Subjects in Studies AI463022 and AI463027

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

a Subjects with evaluable baseline histology (baseline Knodell Necroinflammatory Score ³2).

b ³2-point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.

c For Ishak Fibrosis Score, improvement = ³1-point decrease from baseline and worsening = ³1-point increase from baseline.

* $p<0.05$

Table 5 : Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Nucleoside-Naive Subjects in Studies AI463022 and AI463027

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

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

* p<0.05

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

Lamivudine-refractory subjects

Study AI463026 was a multinational, randomized, double-blind study of BARACLUDE in 286 (of 293 randomized) subjects with lamivudine-refractory chronic hepatitis B infection. Subjects receiving lamivudine at study entry either switched to BARACLUDE 1 mg once daily (with neither a washout nor an overlap period) or continued on lamivudine 100 mg for a minimum of 52 weeks. The mean age of subjects was 39 years, 76% were male, 37% were Asian, 62% were Caucasian, and 52% had previously received interferon-a. The mean duration of prior lamivudine therapy was 2.7 years, and 85% had lamivudine resistance mutations at baseline by an investigational line probe assay. At baseline, subjects had a mean Knodell Necroinflammatory Score of 6.5, mean serum HBV DNA as measured by Roche COBAS Amplicor PCR assay was 9.36 log_{10} copies/mL, and mean serum ALT level was 128 U/L. Paired, adequate liver biopsy samples were available for 87% of subjects.

BARACLUDE was superior to lamivudine on a primary endpoint of Histologic Improvement (using the Knodell Score at Week 48). These results and change in Ishak Fibrosis Score are shown in Table 6. Table 7 shows selected virologic, biochemical, and serologic endpoints.

Table 6: Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Lamivudine-Refractory Subjects in Study AI463026

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

a Subjects with evaluable baseline histology (baseline Knodell Necroinflammatory Score ³2).

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

c For Ishak Fibrosis Score, improvement = ³1-point decrease from baseline and worsening = ³1-point increase from baseline.

* p<0.01

Table 7: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Lamivudine-Refractory Subjects in Study AI463026

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

[a] Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).
* p<0.0001

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

Outcomes Beyond 48 Weeks

The optimal duration of therapy with BARACLUDE is unknown. According to protocol-mandated criteria in the Phase 3 clinical trials, subjects discontinued BARACLUDE or lamivudine treatment after 52 weeks according to a definition of response based on HBV virologic suppression (<0.7 MEq/mL by bDNA assay) and loss of HBeAg (in HBeAg-positive subjects) or ALT <1.25 X ULN (in HBeAg-negative subjects) at Week 48. Subjects who achieved virologic suppression but did not have serologic response (HBeAg-positive) or did not achieve ALT <1.25 X ULN (HBeAg-negative) continued blinded dosing through 96 weeks or until the response criteria were met. These protocol-specified subject management guidelines are not intended as guidance for clinical practice.

Nucleoside-naive subjects: Among nucleoside-naive, HBeAg-positive subjects (Study AI463022), 243 (69%) BARACLUDE-treated subjects and 164 (46%) lamivudine-treated subjects continued blinded treatment for up to 96 weeks. Of those continuing blinded treatment in year 2, 180 (74%) BARACLUDE subjects and 60 (37%) lamivudine subjects achieved HBV DNA <300 copies/mL by PCR at the end of dosing (up to 96 weeks). 193 (79%) BARACLUDE subjects achieved ALT ≤1 X ULN compared to 112 (68%) lamivudine subjects, and HBeAg seroconversion occurred in 26 (11%) BARACLUDE subjects and 20 (12%) lamivudine subjects.

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

Among nucleoside-naive, HBeAg-negative subjects (Study AI463027), 26 (8%) BARACLUDE-treated subjects and 28 (9%) lamivudine-treated subjects continued blinded treatment for up to 96 weeks. In this small cohort continuing treatment in year 2, 22 BARACLUDE and 16 lamivudine subjects had HBV DNA <300 copies/mL by PCR, and 7 and 6 subjects, respectively, had ALT ≤1 X ULN at the end of dosing (up to 96 weeks).

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

Lamivudine-refractory subjects: Among lamivudine-refractory subjects (Study AI463026), 77 (55%) BARACLUDE-treated subjects and 3 (2%) lamivudine subjects continued blinded treatment for up to 96 weeks. In this cohort of BARACLUDE subjects, 31 (40%) subjects achieved HBV DNA <300 copies/mL, 62 (81%) subjects had ALT ≤1 X ULN, and 8 (10%) subjects demonstrated HBeAg seroconversion at the end of dosing.

Special Populations

Study AI463038 was a randomized, double-blind, placebo-controlled study of BARACLUDE versus placebo in 68 subjects co-infected with HIV and HBV who experienced recurrence of HBV viremia while receiving a lamivudine-containing highly active antiretroviral (HAART) regimen. Subjects continued their lamivudine-containing HAART regimen (lamivudine dose 300 mg/day) and were assigned to add either BARACLUDE 1 mg once daily (51 subjects) or placebo (17 subjects) for 24 weeks followed by an open-label phase for an additional 24 weeks where all subjects received BARACLUDE. At baseline, subjects had a mean serum HBV DNA level by PCR of 9.13 log_{10} copies/mL. Ninety-nine percent of subjects were HBeAg-positive at baseline, with a mean baseline ALT level of 71.5 U/L. Median HIV RNA level remained stable at approximately 2 log_{10} copies/mL through 24 weeks of blinded therapy. Virologic and biochemical endpoints at Week 24 are shown in Table 8. 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: Co-infection with HIV**).

Table 8: Virologic and Biochemical Endpoints at Week 24, Study AI463038

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

[a] All subjects also received a lamivudine-containing HAART regimen.
[b] Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).
[c] Percentage of subjects with abnormal ALT (>1 X ULN) at baseline who achieved ALT normalization (n=35 for BARACLUDE and n=12 for placebo).
* p<0.0001

For subjects originally assigned to BARACLUDE, at the end of the open-label phase (Week 48), 8% of subjects had HBV DNA <300 copies/mL by PCR, the mean change from baseline HBV DNA by PCR was -4.20 log_{10} copies/mL, and 37% of subjects with abnormal ALT at baseline had ALT

normalization (≤1 X ULN).

CONTRAINDICATIONS

BARACLUDE 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**).

Co-infection with HIV

BARACLUDE has not been evaluated in HIV/HBV co-infected patients who were not simultaneously receiving effective HIV treatment. Limited clinical experience suggests there is a potential for the development of resistance to HIV nucleoside reverse transcriptase inhibitors if BARACLUDE is used to treat chronic hepatitis B virus infection in patients with HIV infection that is not being treated (see **MICROBIOLOGY: Antiviral Activity**, *Antiviral Activity against HIV*). Therefore, therapy with BARACLUDE is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART). Before initiating BARACLUDE therapy, HIV antibody testing should be offered to all patients. BARACLUDE has not been studied as a treatment for HIV infection and is not recommended for this use.

PRECAUTIONS

General

Renal Impairment

Dosage adjustment of BARACLUDE 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

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

Lamivudine-refractory patients receiving the 1-mg daily dose 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 offered HIV antibody testing before starting BARACLUDE therapy. They should be informed that if they have HIV infection and are not receiving effective HIV treatment, BARACLUDE may increase the chance of HIV resistance to HIV medication (see **WARNINGS: Co-infection with HIV**).

Patients should be advised that treatment with BARACLUDE has not been shown proven to reduce the risk of transmission of HBV to others through sexual contact or blood contamination (see **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 4 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 ³35 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 up to 200 and 16 mg/kg/day and showed no embryotoxicity or maternal toxicity at 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, sternebrae, 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-postnatal 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, BARACLUDE should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits.

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 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 BARACLUDE.

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 subjects 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 2 years. Median duration of therapy was 69 weeks for BARACLUDE-treated subjects and 63 weeks for lamivudine-treated subjects in Studies AI463022 and AI463027 and 73 weeks for BARACLUDE-treated subjects and 51 weeks for lamivudine-treated subjects in Studies AI463026 and AI463014. The safety profiles of BARACLUDE and lamivudine were comparable in these studies. The safety profile of BARACLUDE 1 mg (n=51) in HIV/HBV co-infected subjects enrolled in Study AI463038 was similar to that of placebo (n=17) through 24 weeks of blinded treatment and similar to that seen in non-HIV infected subjects (see **WARNINGS: Co-infection with HIV**).

The most common adverse events of any severity with at least a possible relation to study drug for BARACLUDE-treated subjects were headache, fatigue, dizziness, and nausea. The most common adverse events among lamivudine-treated subjects were headache, fatigue, and dizziness. One percent of BARACLUDE-treated subjects in these four studies compared with 4% of lamivudine-treated subjects discontinued for adverse events or abnormal laboratory test results. 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 BARACLUDE was compared with lamivudine are presented in Table 9.

Table 9: Selected Clinical Adverse Events[a] of Moderate-Severe Intensity (Grades 2-4) Reported in Four Entecavir Clinical Trials Through 2 Years

Body System/ Adverse Event	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
Any Grade 2-4 adverse event[a]	15%	18%	22%	23%
Gastrointestinal				
Diarrhea	<1%	0	1%	0
Dyspepsia	<1%	<1%	1%	0
Nausea	<1%	<1%	<1%	2%
Vomiting	<1%	<1%	<1%	0
General				
Fatigue	1%	1%	3%	3%
Nervous System				
Headache	2%	2%	4%	1%
Dizziness	<1%	<1%	0	1%
Somnolence	<1%	<1%	0	0
Psychiatric				
Insomnia	<1%	<1%	0	<1%

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

b Studies AI463022 and AI463027.

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

Laboratory Abnormalities

Frequencies of selected treatment-emergent laboratory abnormalities reported during therapy in four clinical trials of BARACLUDE compared with

lamivudine are listed in Table 10.

Table 10: Selected Treatment-Emergent[a] Laboratory Abnormalities Reported in Four Entecavir Clinical Trials Through 2 Years

	Nucleoside-Naive[b]		Lamivudine-Refractory[c]	
Test	**BARACLUDE 0.5 mg n=679**	**Lamivudine 100 mg n=668**	**BARACLUDE 1 mg n=183**	**Lamivudine 100 mg n=190**
Any Grade 3-4 laboratory abnormality[d]	35%	36%	37%	45%
ALT >10 X ULN and >2 X baseline	2%	4%	2%	11%
ALT >5.0 X ULN	11%	16%	12%	24%
AST >5.0 X 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 ³2.1 X ULN	2%	2%	3%	3%
Lipase ³2.1 X ULN	7%	6%	7%	7%
Creatinine >3.0 X ULN	0	0	0	0
Confirmed creatinine increase ³0.5 mg/dL	1%	1%	2%	1%
Hyperglycemia, fasting >250 mg/dL	2%	1%	3%	1%
Glycosuria[e]	4%	3%	4%	6%
Hematuria[f]	9%	10%	9%	6%
Platelets <50,000/mm^3	<1%	<1%	<1%	<1%

a On-treatment value worsened from baseline to Grade 3 or Grade 4 for all parameters except albumin (any on-treatment value <2.5 g/dL), confirmed creatinine increase ³0.5 mg/dL, and ALT >10 X ULN and >2 X baseline.

b Studies AI463022 and AI463027.

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

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

e Grade 3 = 3+, large, ³500 mg/dL; Grade 4 = 4+, marked, severe.

f Grade 3 = 3+, large; Grade 4 = ³4+, marked, severe, many.

Among BARACLUDE-treated subjects 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 $\geq$ 2 $\log_{10}$/mL reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations of Hepatitis after Discontinuation of Treatment (see also WARNINGS)

An exacerbation of hepatitis or ALT flare was defined as ALT >10 X ULN and >2 X the subject's reference level (minimum of the baseline or last measurement at end of dosing). For all subjects who discontinued treatment (regardless of reason), Table 11 presents the proportion of subjects in each study who experienced post-treatment ALT flares. In these studies, a subset of subjects was allowed to discontinue treatment at or after 52 weeks if they achieved a protocol-defined response to therapy. If BARACLUDE is discontinued without regard to treatment response, the rate of post-treatment flares could be higher.

Table 11: Exacerbations of Hepatitis During Off-Treatment Follow-up, Subjects in Studies AI463022, AI463027, and AI463026

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

a Reference is the minimum of the baseline or last measurement at end of dosing. Median time to off-treatment exacerbation was 23 weeks for BARACLUDE-treated subjects and 10 weeks for lamivudine-treated subjects.

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.

Postmarketing Experience

The following adverse reaction has been reported during postmarketing use of BARACLUDE. Because this reaction was reported voluntarily from a population of unknown size, it is not possible to reliably estimate its frequency or establish a causal relationship to BARACLUDE exposure.

Skin and subcutaneous tissue disorders:
Rash
Immune system disorders:
Anaphylactoid reaction.

DOSAGE AND ADMINISTRATION
Recommended Dosage
The recommended dose of BARACLUDE for chronic hepatitis B virus infection in nucleoside-treatment-naive adults and adolescents 16 years of age and older is 0.5 mg once daily, with or without food.

The recommended dose of BARACLUDE in adults and adolescents (≥16 years of age) with a history of hepatitis B viremia while receiving lamivudine or known lamivudine resistance mutations is 1 mg once daily, which must be taken on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).

Renal Impairment
In subjects with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased (see **CLINICAL PHARMACOLOGY: Pharmacokinetics,** *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 12. The once-daily dosing regimens are preferred.

Table 12: Recommended Dosage of BARACLUDE in Patients with Renal Impairment

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

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

[b] If administered on a hemodialysis day, administer BARACLUDE after the hemodialysis session

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.

HOW SUPPLIED
BARACLUDE (entecavir) 0.5 mg Tablets are white to off-white, triangular-shaped film-coated tablets, debossed with “BMS” on one side and “1611” on the other side.

BARACLUDE (entecavir) 1 mg Tablets are pink, triangular-shaped film-coated tablets, debossed with “BMS” on one side and “1612” on the other side.

Storage
BARACLUDE Tablets should be stored below 30° C.
Shelf life: 2 years.

Reg. No. BARACLUDE 0.5 mg Tablet, Blister 3x10’s - DKI 0557001717A1
BARACLUDE 1 mg Tablet, Blister 3x10’s - DKI 0557001717B1

HARUS DENGAN RESEP DOKTER

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