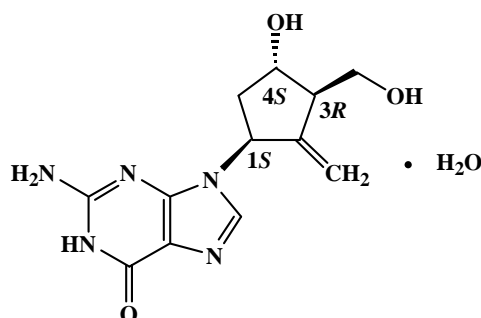


DATA SHEET

Baraclude[®] Tablets and Oral Solution (entecavir)

Name of the medicine

Entecavir is 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 C₁₂H₁₅N₅O₃•H₂O, which corresponds to a molecular weight of 295.3. Entecavir has the following structural formula:



CAS number: 209216-23-9

Description

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, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. The 0.5 mg tablet coating contains titanium dioxide, hypromellose, Macrogol 400, polysorbate 80, and the 1 mg tablet coating contains titanium dioxide, hypromellose, Macrogol 400 and iron oxide red CI177491. 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 anhydrous, methyl hydroxybenzoate, propyl hydroxybenzoate, and orange flavour.

Pharmacology

Pharmacokinetics:

Absorption - In healthy subjects, entecavir was rapidly absorbed with peak plasma concentrations occurring between 0.5 and 1.5 hours. There was a dose-proportionate increase in peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) values following multiple doses ranging from 0.1 to 1 mg. Steady-state was achieved after 6-10 days of once-daily dosing with approximately 2-fold accumulation. C_{max} and trough plasma concentration (C_{trough}) at steady-state were 4.2 and 0.3 ng/mL, respectively, for a 0.5-mg dose, and 8.2 and 0.5 ng/mL, respectively, for a 1-mg dose. In healthy subjects, the bioavailability of the tablet was 100% relative to the oral solution. The oral solution and tablet may be used interchangeably.

Oral administration of entecavir 0.5 mg with a standard high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) resulted in a minimal delay in absorption (1-1.5 hour fed vs. 0.75 hour fasted), a decrease in C_{max} of 44-46%, and a decrease in AUC of 18-20% (see **DOSAGE AND METHOD OF ADMINISTRATION**).

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

Metabolism - Entecavir is not a substrate, inhibitor, or inducer of the CYP450 enzyme system. At concentrations approximately 10,000-fold higher than those obtained in humans, entecavir inhibited none of the major human CYP450 enzymes 1A2, 2C9, 2C19, 2D6, 3A4, 2B6, and 2E1. At concentrations approximately 340-fold higher than those observed in humans, entecavir did not induce the human CYP450 enzymes 1A2, 2C9, 2C19, 3A4, 3A5, and 2B6. Following administration of ^{14}C -entecavir in humans and rats, no oxidative or acetylated metabolites and minor amounts of the phase II metabolites glucuronide and sulfate conjugates were observed.

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

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

Special Populations

Gender/race

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

Elderly

The pharmacokinetic profile of entecavir does not vary by age.

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

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

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, hemodialysis removed approximately 13% of the entecavir dose over 4 hours and 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 and severe hepatic impairment. 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

Entecavir exposure in HBV-infected liver transplant recipients on a stable dose of cyclosporine A or tacrolimus (n=9) 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. Before and during Baraclude therapy in liver transplant recipients receiving cyclosporine or tacrolimus, renal function should be carefully evaluated (see **DOSAGE AND ADMINISTRATION: Renal Impairment.**)

Pediatrics

Pharmacokinetic studies have not been conducted in children.

Drug Interactions (see also PRECAUTIONS: Drug Interactions)

Entecavir is not a substrate, inhibitor, or inducer of the CYP450 enzyme system (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 each of the following:

- lamivudine,
- adefovir dipivoxil,
- tenofovir disoproxil fumarate.

A pilot study in nine HBV-infected liver transplant recipients suggested that concurrent cyclosporine A (n=5) or tacrolimus (n=4) therapy did not affect the pharmacokinetics of entecavir (see **Special Populations, Post-Liver Transplant**). The effect of entecavir on the pharmacokinetics of cyclosporine A or tacrolimus is unknown.

Pharmacological actions

Mechanism of action - Entecavir is a guanosine nucleoside analogue with potent and selective activity against HBV polymerase. It is phosphorylated to the active triphosphate (TP) form, which has an intracellular half-life of 15 hours. Intracellular TP levels are directly related to extracellular entecavir concentrations, with no significant accumulation beyond initial plateau levels. By competing with the natural substrate deoxyguanosine TP, entecavir-TP functionally inhibits all 3 activities of the viral polymerase: (1) priming of the HBV polymerase, (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand HBV DNA. The entecavir-TP K_i for HBV DNA polymerase is 0.0012 μM . Entecavir-TP is a weak inhibitor of cellular DNA polymerases α , β , and δ with K_i values of 18 to 40 μM . In addition, high exposures of entecavir had no relevant adverse effects on γ polymerase or mitochondrial DNA synthesis in HepG2 cells ($K_i > 160 \mu\text{M}$).

Resistance in vitro - There was reduced susceptibility to entecavir when LVD^R substitutions were present. Entecavir inhibited the replication of LVD^R HBV at 8-fold higher concentrations than that for the wild-type virus in cell-based studies. At extracellular concentrations representative of plasma levels achieved with 1mg dosing, intracellular entecavir-TP would be expected to surpass those needed to inhibit the enzyme activity of lamivudine-resistant HBV polymerases. Recombinant viruses encoding adefovir-resistant substitutions at either rtN236T or rtA181V remained fully susceptible to entecavir.

Clinical resistance - patients in clinical trials initially treated with entecavir 0.5mg (nucleoside-naïve) or 1.0mg (lamivudine-refractory) and with an on-therapy PCR HBV DNA measurement at or after Week 24 were monitored for resistance. Virologic rebounds due to resistance to entecavir require the prior existence of primary LVD^r substitutions (M204I/V \pm L180M) along with an additional substitution at residues T184, S202, and/or M250 of the polymerase protein.

Nucleoside-naïve studies: Through Week 240 in nucleoside-naïve studies evidence of entecavir resistance (ETV^r) substitutions at rtT184, rtS202, or rtM250 was identified in 3 patients treated with entecavir, 2 of whom experienced virologic breakthrough as shown in Table 2. These

substitutions were observed only in the presence of LVDr substitutions (rtM204V/I±rtL 180M). The cumulative probability of emerging genotypic ETVr substitutions in nucleoside-naive studies was 0.2%, 0.5%, 1.2%, 1.2% and 1.2% through Year 1, Year 2, Year 3, Year 4 and Year 5 respectively.

Table 2. Emerging Genotypic Resistance Through Year 5, Nucleoside-Naive Studies

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

^a Results in Year 3 reflect use of a 1-mg dose of entecavir for 147 of 149 patients in Year 3 and all patients in Years 4 and 5 and of combination entecavir-lamivudine therapy (followed by long-term entecavir therapy) for a median of 20 weeks for 130 of 149 patients in Year 3 and for 1 week for 1 of 121 patients in Year 4 in a rollover study.

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

^c Patient also have LVDr substitutions

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

Lamivudine-refractory studies ETVr substitutions (in addition to LVDr substitutions rtM204V/I ± rtL180M) were observed at baseline in isolates from 10 (5%) of 187 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 240, 3 of these 10 patients experienced virologic breakthrough ($\geq \log_{10}$ increase above nadir). Emerging entecavir resistance in lamivudine-refractory studies through Week 240 is summarised below in the Table 3.

Table 3: Emerging Genotypic Entecavir Resistance through Year 5, Lamivudine-Refractory Studies

| | Year 1 | Year 2 | Year3 ^a | Year4 ^a | Year5 ^a |
|--|-----------------|------------------|--------------------|--------------------|--------------------|
| Patients treated and monitored for resistance | 187 | 146 | 80 | 52 | 33 |
| Patients in specific year with: | | | | | |
| - emerging genotypic ETVr ^c | 11 | 12 | 16 | 6 | 2 |
| - genotypic ETVr ^c with virologic breakthrough ^d | 2 ^e | 14 ^e | 13 ^e | 9 ^e | 1 ^e |
| Cumulative probability of: | | | | | |
| -emerging genotypic ETVr ^c | 6% | 15% | 36% | 47% | 51% |
| - genotypic ETVr ^c with virologic breakthrough ^d | 1% ^e | 11% ^e | 27% ^e | 41% ^e | 44% ^e |

^a Results reflect use of a combination entecavir-lamivudine therapy (followed by long-term entecavir therapy) for a median of 13 weeks for 48 of 80 patients in Year 3, a median of 38 weeks for 10 of 52 patients in Year 4, and for 16 weeks for 1 of 33 patients in Year 5 in a rollover study.

^b Includes patients with at least one on-therapy HBV DNA measurement by PCR at or after week 24 through week 58 (Year 1), after week 58 through week 102 (Year 2), after week 102 through week 156 (Year 3), after week 156 through week 204 (Year4) , or after week 204 through week 252 (Year 5).

^c Patients also have LVDr substitutions.

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

^e ETVr occurring in any year, virologic breakthrough in specified year.

Clinical Trials

The safety and efficacy of Baraclude were evaluated in four active-controlled trials on five continents. These studies included 1720 patients 16 years of age or older with chronic hepatitis B infection (serum HBsAg-positive for at least 6 months) accompanied by evidence of viral replication (detectable serum HBV DNA, as measured by the bDNA hybridization or PCR assay). Subjects in Phase 3 Studies AI463022, AI463026, and AI463027 had persistently elevated ALT levels ≥ 1.3 times the upper limit of normal (ULN) and chronic inflammation on liver biopsy compatible with a diagnosis of chronic viral hepatitis, whereas abnormal ALT was not an entry criterion and liver biopsy was optional in the Phase 2 Study AI463014. The safety and efficacy of Baraclude were also evaluated in an active-controlled study of 191 HBV-infected patients with decompensated liver disease and 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 (range 16 to 78), and 75% were male; 57% were Asian, 40% were Caucasian, and 13% had previously received interferon- α treatment. At baseline, patients had a mean Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA level as measured by Roche COBAS Amplicor[®] PCR assay of 9.66 \log_{10} copies/mL, and mean serum ALT level of 143 U/L. Paired adequate liver biopsy samples were collected 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 (presumed to have pre-core or core-promoter mutants). The mean age of patients was 44 years (range 18 to 77), and 76% were male. Thirty-nine percent were Asian and 58% were Caucasian; 13% had previously received interferon- α treatment. At baseline, patients had a mean Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA level as measured by Roche COBAS Amplicor PCR assay of 7.58 \log_{10} copies/mL, and mean serum ALT level of 141.7 U/L. Ninety-eight percent of patients had a baseline liver biopsy, and 89% had a biopsy at Week 48; paired samples were collected for 88% of patients. Response was assessed at Week 52 based on test results obtained at the Week 48 visit.

In Studies AI463022 and AI463027, Baraclude was superior to lamivudine on the primary efficacy endpoint of Histologic Improvement, defined as ≥ 2 -point reduction in Knodell Necroinflammatory Score with no worsening in Knodell Fibrosis Score at Week 48. Histologic Improvement and change in Ishak Fibrosis Score are shown in Table 4. Biochemical, virologic, and serologic outcome measures are shown in Table 5.

Table 4: 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) | | |
|--|--|---|---|---|---|---|
| | Bara- clude 0.5 mg n=314 ^a | Lami- vudine 100 mg n=314 ^a | Difference Baraclude- lamivudine (95% CI) ^b | Baraclude 0.5 mg n=296 ^a | Lami- vudine 100 mg n=287 ^a | Difference Baraclude- lamivudine (95% CI) ^b |
| Histologic Improvement (Knodell Scores) | | | | | | |
| Improvement ^c | 72% | 62% | 9.9% ^d (2.6%, 17.2%) | 70% | 61% | 9.6% ^e (2.0%, 17.3%) |
| No improvement | 21% | 24% | | 19% | 26% | |
| Ishak Fibrosis Score^f | | | | | | |
| Improvement ^f | 39% | 35% | 3.2% ^g (-4.4%, 10.7%) | 36% | 38% | -1.8% ^g (-9.7%, 6.0%) |
| No change | 46% | 40% | | 41% | 34% | |
| Worsening ^f | 8% | 10% | | 12% | 15% | |
| Inadequate Week 48 biopsy | 2% | 5% | | 2% | 1% | |
| Missing Week 48 biopsy | 5% | 9% | | 8% | 11% | |

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

^b In these analyses, missing or inadequate biopsies at Week 48 were classified “no improvement.”

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

^d $p < 0.01$.

^e $p < 0.05$.

^f For Ishak Fibrosis Score, improvement = ≥ 1 -point decrease from baseline and worsening = ≥ 1 -point increase from baseline.

^g Not significant.

CI = confidence interval.

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

| | Study AI463022 (HBeAg-Positive) | | | Study AI463027 (HBeAg-Negative) | | |
|---|-----------------------------------|------------------------------------|--|---------------------------------|------------------------------------|--|
| | Bara- clude 0.5 mg n=354 | Lami- vudine 100 mg n=355 | Difference Baraclude- lamivudine (95% CI) | Baraclude 0.5 mg n=325 | Lami- vudine 100 mg n=313 | Difference Baraclude- lamivudine (95% CI) |
| ALT normalization ($\leq 1 \times \text{ULN}$) | 68% | 60% | 8.4% ^a (1.3%, - 15.4%) | 78% | 71% | 6.9% ^a (0.2%, - 13.7%) |
| HBV DNA Mean change from baseline by PCR ^b (log ₁₀ copies/mL) | -6.86 | -5.39 | -1.52 ^c (-1.8, - 1.3) | -5.04 | -4.53 | -0.43 ^c (-0.6, - 0.3) |
| Proportion undetectable (< 300 copies/mL) by PCR ^{b,d} | 67% | 36% | 30.3% ^c (23.3%, 37.3%) | 90% | 72% | 18.3% ^e (12.3%, 24.2%) |
| < 0.7 MEq/mL by bDNA ^f | 91% | 65% | 25.6% ^e (19.8%, 31.4%) | 95% | 89% | 5.9% ^f (1.8%, 10.1%) |
| Loss of HBeAg | 22% | 20% | | N/A | N/A | |
| HBeAg seroconversion | 21% | 18% | | N/A | N/A | |

^a $p < 0.05$.

^b Roche COBAS Amplicor PCR assay.

^c $p < 0.0001$.

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

^e Quantiplex bDNA assay.

^f $p < 0.01$.

CI = confidence interval.

Responses for patients with baseline Knodell Fibrosis Scores of 4 (cirrhosis) were comparable to overall responses on all efficacy outcome measures (all patients had compensated liver disease). Histologic Improvement was independent of baseline HBV DNA or ALT levels.

Covalently closed circular deoxyribonucleic acid (cccDNA) is a stable genomic form of nuclear HBV DNA that serves as a hepatic reservoir of virus, provides the template for HBV transcription, and contributes to viral persistence and relapse. For a subset of patients with paired liver samples in Study AI463022, the mean change from baseline in hepatic cccDNA at Week 48 was $-0.9 \log_{10}$ copies/human genome equivalents (approximately 8-fold reduction) for Baraclude-treated patients ($n=159$) and $-0.7 \log_{10}$ copies/HGEq (approximately 5-fold reduction) for lamivudine-treated patients ($n=146$). In Study AI463027, the mean change from baseline in hepatic cccDNA at Week 48 was $-0.5 \log_{10}$ copies/HGEq (approximately 3-fold reduction) in each treatment group ($n=107$ for Baraclude-treated patients and $n=104$ for lamivudine-treated patients).

Outcomes Beyond 48 weeks

HBeAg-positive

Through 96 weeks, cumulative confirmed outcomes for HBeAg-positive patients (all treated) demonstrate that continued treatment with entecavir (n=354) resulted in an increase in the proportion of patients with HBV DNA < 300 copies/mL by PCR (80%) and ALT normalization (≤ 1 times ULN) (87%). Through the last observation on or off treatment, 31% of entecavir -treated patients had HBeAg seroconversion and 5% had HBsAg loss. In the lamivudine treatment group (n=355), cumulative confirmed HBV DNA < 300 copies/mL by PCR occurred in 39% of patients and ALT normalization in 79%; 26% of patients had HBeAg seroconversion and 3% had HBsAg loss. The difference between treatment groups was statistically significant for percentage of patients with HBV DNA < 300 copies/mL and ALT normalization ($p < 0.01$).

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

HBeAg-negative

Through 96 weeks for HBeAg-negative patients, 94% of entecavir -treated patients (n=325) and 77% of lamivudine-treated patients (n=313) had cumulative confirmed HBV DNA < 300 copies/mL ($p < 0.01$). ALT normalization (≤ 1 times ULN) occurred in 89% of entecavir -treated patients and 84% of lamivudine-treated patients.

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

Liver biopsy results: Of the 679 entecavir monohydrate-treated patients in the two nucleoside-naïve studies, 293 (43%) eligible patients enrolled in a long-term rollover study and continued entecavir monohydrate therapy. Patients in the rollover study received entecavir monohydrate 1 mg once daily. Sixty-nine of the 293 patients elected to have a repeat liver biopsy after a total treatment duration of more than 144 weeks (3 years). Fifty-seven patients had both an evaluable baseline and long-term biopsy, with a median duration of entecavir monohydrate therapy of 280 weeks (approximately 6 years). Ninety-six percent of these patients had Histologic Improvement (a ≥ 2 -point decrease in Knodell necroinflammatory score from baseline with no worsening of the Knodell fibrosis score), and 88% had a ≥ 1 -point decrease in Ishak fibrosis score. Of the 43 patients with a baseline Ishak fibrosis score of ≥ 2 , 58% had a ≥ 2 point decrease. All (10/10) patients with advanced fibrosis or cirrhosis at baseline (Ishak fibrosis score of 4,5 or 6) had a ≥ 1 point decrease (median decrease from baseline of 1.5 points). At the time of the long-term biopsy, 57 (100%) of patients had HBV DNA < 300 copies/mL and 49 (86%) had serum ALT ≤ 1 X ULN.

Lamivudine-Refractory Patients

Study AI463026 was a multinational, randomized, double-blind study of Baraclude in 286 (of 293 randomized) patients with lamivudine-refractory chronic hepatitis B infection. Patients receiving lamivudine at study entry either switched to Baraclude 1 mg once daily or continued on lamivudine 100 mg for 52 weeks. The mean age of patients was 39 years (range 16 to 74), and 76% were male; 37% were Asian and 62% were Caucasian. Eighty-five percent had LVD^R mutations at baseline. Patients had a mean Knodell Necroinflammatory Score of 6.5, mean serum HBV DNA level as measured by Roche COBAS Amplicor PCR assay of 9.36 log₁₀ copies/mL, and mean serum ALT level of 128 U/L. Response was assessed at Week 52 based on test results obtained at the Week 48 visit. Ninety-eight percent of patients had a baseline liver biopsy, and 88% had a biopsy at Week 48; paired samples were collected for 87% of patients.

In Study AI463026, Baraclude was superior to lamivudine on the coprimary endpoints of Histologic Improvement (using the Knodell Score at Week 48) and Composite Endpoint (proportion of patients with HBV DNA <0.7 MEq/mL by bDNA assay and ALT <1.25 ULN at Week 48). These results and change in Ishak Fibrosis Score are shown in Table 6. Table 7 shows biochemical, virologic, and serologic endpoints for Studies AI463026.

Table 6: Histologic Improvement, Change in Ishak Fibrosis Score, and Composite Endpoint at Week 48, Lamivudine-Refractory Patients in Study AI463026^a

| | Baraclude 1 mg n=124 ^a | Lamivudine 100 mg n=116 ^a | Difference Baraclude- lamivudine (97.5% CI) |
|--|---|--|--|
| Histologic Improvement (Knodell Scores) | | | |
| Improvement ^b | 55% | 28% | 27.3% ^{c,d} (13.6%, 40.9%) |
| No improvement | 34% | 57% | |
| Ishak Fibrosis Score^e | | | |
| Improvement ^e | 34% | 16% | 17.5% ^{c,f} (6.8%, 28.2%) ^g |
| No change | 44% | 42% | |
| Worsening ^e | 11% | 26% | |
| Inadequate Week 48 biopsy | 2% | 1% | |
| Missing Week 48 biopsy | 10% | 15% | |
| Composite Endpoint^h | n=141 55% | n=145 4% | 50.5% ^d (40.4%, 60.6%) |

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

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

^c In this analysis, missing or inadequate biopsies at Week 48 were classified “no improvement.”

^d $p < 0.0001$.

^e For Ishak Fibrosis Score, improvement = ≥ 1 -point decrease from baseline and worsening = ≥ 1 -point increase from baseline.

^f $p < 0.01$.

^g 95% confidence interval.

^h Composite Endpoint (a coprimary endpoint) was defined as HBV DNA <0.7 MEq/mL by bDNA assay and serum ALT (<1.25 X ULN) at Week 48.

CI = confidence interval

Table 7: Biochemical, Virologic, and Serologic Endpoints at Week 48, Lamivudine-Refractory Patients in Studies AI463026

| Phase 3 Study AI463026 | | | |
|--|---------------------------------|------------------------------------|--|
| | Bara- clude 1 mg N=141 | Lami- vudine 100 mg n=145 | Difference Baraclude- lamivudine (95% CI) |
| ALT normalization ($\leq 1 \times$ ULN) | 61% | 15% | 45.8% ^b (35.9%, 55.8%) |
| HBV DNA Mean change from baseline by PCR ^b (log ₁₀ copies/mL) | -5.11 | -0.48 | -4.39 ^a (-4.8, -4.0) |
| Proportion undetectable (< 300 copies/ mL) by PCR ^{b,c} | 19% | 1% | 17.8% ^a (11.0%, 24.5%) |
| < 0.7 MEq/mL by bDNA ^d | 66% | 6% | 60.4% ^a (51.8%, 69.1%) |
| Loss of HBeAg | 10% | 3% | |
| HBeAg seroconversion | 8% | 3% | |

^a $p < 0.0001$.

^b Roche COBAS Amplicor PCR assay.

^c At Week 24, HBV DNA < 300 copies/mL by PCR was observed in 7% of Baraclude-treated patients and no lamivudine-treated patients ($p = 0.0011$) in Study AI463026 and 12% of Baraclude-treated patients and 2% of lamivudine-treated patients ($p = 0.0749$) in Study AI463014.

^d Quantiplex bDNA assay.

CI = confidence interval.

In Study AI463026, responses for patients with baseline Knodell Fibrosis Scores of 4 (cirrhosis) were comparable to overall responses on all efficacy outcome measures (all patients had compensated liver disease). Histologic Improvement was independent of baseline HBV DNA or ALT levels.

For a subset of patients with paired liver samples in Study AI463026, the mean change from baseline in hepatic cccDNA at Week 48 was $-0.6 \log_{10}$ copies/HGEq (approximately 4-fold reduction) for Baraclude-treated patients ($n = 74$) and $0.0 \log_{10}$ copies/HGEq for lamivudine-treated patients ($n = 59$).

Health-related quality of life (HRQoL) was assessed in Study AI463026 using the standardized and validated EQ-5D instrument developed by the EuroIQoL group. After 48 weeks of therapy, Baraclude-treated patients experienced significantly less worsening compared to lamivudine-treated patients in the dimensions of mobility, self care, and pain/discomfort.

Outcomes beyond 48 weeks

Cumulative confirmed outcomes through 96 weeks for all treated lamivudine-refractory patients (n=141) demonstrate that continued treatment with entecavir resulted in an increase in the proportion of patients with HBV DNA <300 copies/mL by PCR (30%) and ALT normalization (≤ 1 times ULN) (85%). Through the last observation on or off treatment, 17% of entecavir - treated patients had HBeAg seroconversion. The difference between the entecavir and lamivudine treatment groups was statistically significant on all three parameters ($p < 0.01$).

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

Post-Treatment Follow-up

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

Special Populations

Patients with Decompensated Liver Disease

Study AI463048 was a randomized, open-label study of Baraclude versus adefovir dipivoxil in 191 (of 195 randomised) patients with HBeAg-positive or –negative chronic HBV infection and evidence of hepatic decompensation, defined as Child-Turcotte-Pugh (CTP) score of 7 or higher. Patients were either HBV-treatment naïve or pretreated (excluding pretreatment with Baraclude, adefovir dipivoxil, or tenofovir disoproxil fumarate). At baseline, patients had a mean serum HBV DNA by PCR of 7.83 \log_{10} copies/mL and mean ALT level of 100 U/L; 54% of patients were HBeAg-positive; 35% had genotypic evidence of lamivudine resistance. The baseline mean CTP score was 8.6. The dose of Baraclude in this study was 1 mg once daily. Baraclude was superior to adefovir dipivoxil on the primary efficacy endpoint of mean change from baseline in serum HBV DNA by PCR at Week 24. Results for selected study endpoints at Weeks 24 and 48 are shown in Table 8.

Table 8: Selected Endpoints at Weeks 24 and 48, Patients with Decompensated Liver Disease, Study AI463048.

| | Week 24 | | Week 48 | |
|--|-----------------------|--------------------------------|-----------------------|--------------------------------|
| | Baraclude 1mg (n=100) | Adefovir Dipivoxil 10mg (n=91) | Baraclude 1mg (n=100) | Adefovir Dipivoxil 10mg (n=91) |
| HBV DNA ^a | | | | |
| Proportion undetectable (<300 copies/mL) | 49%* | 16% | 57%* | 20% |
| Mean change from baseline (log ₁₀ copies/mL) | -4.48* | -3.40 | -4.66 | -3.90 |
| Stable or improved CTP score ^b | 66% | 71% | 61% | 67% |
| Model for End-Stage Liver Disease (MELD) score Mean change from baseline ^c | -2.0 | -0.9 | -2.6 | -1.7 |
| HBsAg loss | 1% | 0 | 5% | 0 |
| Normalisation of: ^d | | | | |
| ALT (≤1 X ULN) | 46/78 (59%)* | 28/71 (39%) | 49/78 (63%)* | 33/71 (46%) |
| Albumin (≥1 X LLN) | 20/82 (24%) | 14/69 (20%) | 32/82 (39%) | 20/69 (29%) |
| Bilirubin (≤1 X ULN) | 12/75 (16%) | 10/65 (15%) | 15/75 (20%) | 18/65 (28%) |
| Prothrombin time (≤1 X ULN) | 9/95 (9%) | 6/82 (7%) | 8/95 (8%) | 7/82 (9%) |

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

^b Defined as decrease or no change from baseline in CTP score

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

^d Denominator is patients with abnormal values at baseline

* p<0.05

ULN = upper limit of normal, LLN = lower limit of normal

HIV/HBV Co-infected Patients

Study AI463038 was a randomized, double-blind, placebo-controlled study of Baraclude versus placebo in 68 patients co-infected with HIV and HBV who were lamivudine refractory (experienced recurrence of HBV viremia while receiving a lamivudine-containing HAART [highly active antiretroviral therapy] 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 log₁₀ copies/mL. Most patients were HBeAg-positive at baseline, with a mean baseline ALT level of 71.5 U/L. Biochemical and virologic endpoints at Week 24 are shown in Table 9.

| | Baraclude 1 mg^a n=51 | Placebo^a n=17 | Difference Baraclude- Placebo (95% CI) |
|---|--|-------------------------------------|---|
| HBV DNA (by PCR assay ^b) | | | |
| Proportion undetectable (≤ 300 copies/mL) | 6% | 0 | 5.9% (-0.6, 12.3) |
| mean change from baseline (log ₁₀ copies/mL) | -3.65 | +0.11 | -3.75 ^c (-4.47, -3.04) |
| ALT normalization ($\leq 1 \times$ ULN) ^d | 34% | 8% | 26.0 ^e (3.8, 48.1) |

^a All patients also received a lamivudine-containing HAART regimen.

^b Roche COBAS Amplicor PCR assay.

^c p<0.0001.

^d n=35 for baraclude and n=12 for placebo.

^e p=0.08

At the end of the open-label phase (Week 48), the mean change from baseline HBV DNA by PCR for patients originally assigned to entecavir was -4.20 log₁₀ copies/mL; 8% of patients had HBV DNA <300 copies/mL by PCR; and 37% of patients with abnormal ALT at baseline had ALT normalization (≤ 1 times ULN). Entecavir has not been evaluated in HIV/HBV co-infected patients who are not concurrently receiving effective HIV treatment (see **Precautions - Coinfection with HIV**).

Indications

Baraclude is indicated for the treatment of chronic HBV infection in adults with evidence of active liver inflammation.

Contraindications

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

Precautions

Lactic acidosis

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

Exacerbations of hepatitis after discontinuation of treatment

Acute exacerbation of hepatitis has been reported in patients who have discontinued hepatitis B therapy, including therapy with Baraclude (see **Adverse Effects**). The majority of post-treatment exacerbations appear to be self-limited. However, severe exacerbations, including fatalities, may occur. The causal relationship of these events to discontinuation of therapy is unknown. Hepatic function should be monitored at repeated intervals after discontinuation. If appropriate, resumption of hepatitis B therapy may be warranted.

Patients with renal impairment

Dosage adjustment of Baraclude is recommended for patients with renal impairment (see **Pharmacokinetics - Patients with renal impairment**).

Liver transplant recipients

Renal function should be carefully evaluated before and during Baraclude therapy in liver transplant recipients receiving cyclosporine or tacrolimus (see – **Dosage and Administration - Patients with hepatic impairment**, and **Pharmacokinetics - Patients with hepatic impairment**, and - *Liver transplant recipients*).

Decompensated liver disease

A study of Baraclude at a dose of 1 mg once daily has been conducted in patients with decompensated liver disease (see **Clinical Trials** and **Adverse Reactions**).

Co-infection with hepatitis C or D

There are no data on the efficacy of Baraclude in patients co-infected with hepatitis C or D.

Lactose

This medicinal product contains 120.5 mg of lactose in each 0.5 mg daily dose and 241 mg of lactose in each 1 mg daily dose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine.

Co-infection with HIV

Baraclude has not been evaluated in HIV/HBV co-infected patients not simultaneously receiving HIV treatment. Therapy with Baraclude is not recommended in HIV/HBV co-infected patients not receiving HAART. Limited clinical experience suggests that 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.

Patient information

A Consumer Medicine Information Leaflet 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**).

Use in Pregnancy - Pregnancy Category B3

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

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

When entecavir was orally administered to presumed-pregnant rats, no drug-related changes were observed in either dams or fetuses at maternal exposures approximately 50 times human exposure at 0.5 mg/day (28 times at 1 mg/day). At maternal exposures \geq 318 human exposure at 0.5 mg/day (\geq 180 times at 1 mg/day), embryo-fetal toxicity (resorptions) and maternal toxicity were observed, and at exposure 5498 times human exposure at 0.5 mg/day (3100 times at 1 mg/day), lower fetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternbrae, and phalanges), and extra lumbar vertebrae and ribs were observed. When entecavir was orally administered to presumed-pregnant rabbits, no drug-related developmental changes were noted at systemic exposures up to 377 times that in humans at 0.5 mg/day (212 times at 1 mg/day). At exposure 1566 times human exposure at 0.5 mg/day (883 times at 1 mg/day), embryo-fetal toxicity (resorptions), reduced ossification (hyoid), and an increased

incidence of 13th rib were observed. In an oral study of prenatal and postnatal development in rats, entecavir did not affect offspring at exposures >165 times human exposure at 0.5 mg/day (>94 times at 1 mg/day).

Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to entecavir, a Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 0800 167 567.

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.

Use in Lactation

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

Pediatric use

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

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. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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**).

Carcinogenicity, mutagenesis and impairment of fertility

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

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

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

Drug Interactions

Medicinal products: Since entecavir is predominantly eliminated by the kidney (see Excretion), coadministration with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of either medicinal product.

Coadministration of entecavir with lamivudine, adefovir dipivoxil or tenofovir disoproxil fumarate resulted in no significant drug interactions. The effects of coadministration of entecavir with other medicinal products that are excreted renally or affect renal function have not been evaluated. Patients should be monitored closely for adverse events when Baraclude is coadministered with such medicinal products.

Food: Administration of entecavir with food decreased absorption. (See Dosage and Administration and Pharmacokinetics – Absorption).

Adverse Reactions

Assessment of adverse reactions is based on four clinical studies in which 1720 patients with chronic HBV infection received double-blind treatment with Baraclude 0.5 mg/day (n = 679), Baraclude 1 mg/day (n = 183), or lamivudine (n = 858) for up to 107 weeks. The safety profiles of Baraclude and lamivudine were comparable in these studies. Among Baraclude-treated patients, the most common adverse events of any severity with at least a possible relation to Baraclude were headache (9%), fatigue (6%), dizziness (4%) and nausea (3%).

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

Clinical events

Nucleoside-naive patients: In two double-blind, lamivudine-controlled studies, one with patients who tested positive for the hepatitis B e antigen (HBeAg) and one with HBeAg-negative patients, 679 nucleoside-naive patients received Baraclude 0.5 mg once daily for a median of 53 weeks. Adverse reactions of moderate intensity or greater and considered at least possibly related to treatment with Baraclude are listed by body system organ class. Frequency is defined as very common ($\geq 1/10$); common ($\geq 1/100, < 1/10$); uncommon ($\geq 1/1,000, < 1/100$).

| | |
|--|---|
| <i>Psychiatric disorders:</i> | uncommon: insomnia |
| <i>Nervous system disorders:</i> | common: headache uncommon: dizziness, somnolence |
| <i>Gastrointestinal disorders:</i> | uncommon: nausea, diarrhea, dyspepsia, vomiting |
| <i>General disorders and administration site conditions:</i> | common: fatigue |

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

| | |
|--|-----------------------------|
| <i>Nervous system disorders:</i> | common: headache |
| <i>Gastrointestinal disorders:</i> | common: diarrhea, dyspepsia |
| <i>General disorders and administration site conditions:</i> | common: fatigue |

Laboratory findings

Table 10 shows laboratory findings from four double-blind, lamivudine-controlled clinical studies in which 679 nucleoside-naive patients received Baraclude 0.5 mg once daily for a median of 53 weeks and 183 lamivudine-refractory patients received Baraclude 1 mg for a median of 69 weeks.

Table 10: Selected Laboratory Abnormalities Reported During Treatment in Four Clinical Trials

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

Median duration of therapy was 53 weeks.

^b Median duration of therapy was 69 weeks

ULN=upper limit of normal.

Among Baraclude-treated patients in these studies, on-treatment ALT elevations >10 X ULN and >2 X baseline generally resolved with continued treatment. A majority of these exacerbations were associated with a >2 log₁₀/mL reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations of hepatitis after discontinuation of treatment: Acute exacerbations of hepatitis have been reported in patients who have discontinued anti-HBV therapy, including therapy with Baraclude. The frequency of exacerbation of hepatitis or ALT flare (defined as ALT >10X ULN and 2X the patient's reference level) during off-treatment follow-up in clinical studies with Baraclude is presented in Table 11.

Table 11: Exacerbation of Hepatitis During Off-Treatment Follow-up in Three Clinical Trials

| | Patients with ALT Elevations >10 X ULN and > 2X Reference ^a | |
|-----------------------|--|--------------|
| | Baraclude | Lamivudine |
| Nucleoside-naive | 28/476 (6%) | 43/417 (10%) |
| HBeAg-positive | 4/174 (2%) | 13/147 (9%) |
| HBeAg-negative | 24/302 (8%) | 30/270 (11%) |
| Lamivudine-refractory | 6/52 (12%) | 0/16 |

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

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

Patients with Decompensated Liver Disease

Clinical adverse reactions not otherwise listed under Adverse Reactions that were observed through Week 48 in Study AI463048 in which Baraclude 1mg once daily was compared with adefovir dipivoxil in patients with chronic hepatitis B infection and decompensated liver disease include blood bicarbonate decreased (2% for Baraclude and 0 for adefovir dipivoxil) and renal failure (<1% for Baraclude and 2% for adefovir dipivoxil).

In Study AI463048, on-study cumulative death rates were 23% (23/102) for patients treated with Baraclude and 33% (29/89) for patients treated with adefovir dipivoxil. Causes of death were generally liver-related, as expected in this population. On-study cumulative rates of hepatocellular carcinoma (HCC) were 12% (12/102) for Baraclude and 20% (18/89) for adefovir dipivoxil. The time to onset of HCC or death (whichever occurred first) was comparable in the two treatment groups.

Laboratory test abnormalities: Through week 48 among entecavir monohydrate-treated patients, none had ALT elevations both > 10 times ULN and > 2 times baseline, and 1% of patients had ALT elevations > 2 times baseline together with total bilirubin > 2 times ULN and > 2 times baseline. Albumin levels < 2.5 g/dl occurred in 30% of patients, lipase levels > 3 times baseline in 10% and platelets < 50,000/mm³ in 20%.

Postmarketing experience

The following events have been identified during postapproval use of Baraclude. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Immune system disorders: anaphylactoid reaction

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

Hepatobiliary disorders: increased transaminases

Skin and subcutaneous tissue disorders: alopecia, rash.

Dosage and Administration

Recommended Dosage

The recommended oral dose of Baraclude in adults and adolescents older than 16 years is 0.5 mg once daily. For lamivudine-refractory patients [patients with evidence of viremia while on therapy with lamivudine or the presence of LVD^R (YMDD) mutations], the recommended dose is 1 mg once daily.

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

Baraclude Oral Solution contains 0.05 mg of entecavir per milliliter. Therefore, 10 mL of the oral solution provides a 0.5 mg dose and 20 mL provides a 1-mg dose of entecavir.

Renal Impairment

In patients with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased (see **CLINICAL PHARMACOLOGY: Special Populations**). Dosage adjustment is recommended for patients with creatinine clearance <50 mL/min, including patients on hemodialysis or CAPD, as shown in Table 12 and 13.

Dosing in renal impairment with tablets:

Table 12: Recommended Dosage of Baraclude in Patients with Renal Impairment, Schedule-Based Method

| 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 | 0.5 mg every 48 hours | 1.0mg every 48 hours |
| 10 to <30 | 0.5 mg every 72 hours | 1.0mg every 72 hours |
| <10 | 0.5mg every 5 to 7 days | 1.0mg every 5 to 7 days |
| Hemodialysis or CAPD* | 0.5 mg every 5 to 7 days | 1.0mg every 5 to 7 days |

*On haemodialysis days administer after hemodialysis.

Dosing in renal impairment with Oral Solution:**Table 13: Recommended Dosage of Baraclude in Patients with Renal Impairment, Dose Reduction Method**

| Creatinine Clearance (mL/min) | Usual Dose (0.5 mg) | Lamivudine Refractory (1 mg) |
|--------------------------------------|---------------------------------|-------------------------------------|
| ≥50 | 0.5 mg once daily | 1.0 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 | 0.05mg once daily [§] | 0.1mg once daily [§] |
| Hemodialysis or CAPD* | 0.05 mg once daily | 0.1 mg once daily |

[§] For doses <0.5mg Baraclude Oral Solution is recommended. Do not split tablets

*On haemodialysis days administer after hemodialysis.

Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

Duration of Therapy

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

Overdosage

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

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

Presentation

Baraclude (entecavir) Tablets and Oral Solution are available in the following strengths:

| Product Strength and Dosage Form | Description | Quantity |
|----------------------------------|--|--------------------------|
| 0.5-mg film-coated tablet | White to off-white, triangular-shaped tablet, debossed with “BMS” on one side and “1611” on the other side | Blister Packs 30 tablets |
| 1.0-mg film-coated tablet | Pink, triangular-shaped tablet, debossed with “BMS” on one side and “1612” on the other side. | Blister Packs 30 tablets |
| 0.05-mg/mL oral solution* | Ready-to-use orange-flavored, clear, colorless to pale yellow aqueous solution in a 260-mL bottle. | 210 mL (*not marketed) |

Baraclude Oral Solution is a ready-to-use product; dilution or mixing with water or any other solvent or liquid product is not recommended. Each bottle of the oral solution is accompanied by a dosing spoon that is calibrated in 1-mL increments up to 10 mL. Rinsing of the dosing spoon with water is recommended after each daily dose.

Storage Conditions:

Baraclude Tablets: Store below 30⁰C. Store in original package.

Baraclude Oral Solution : Store below 30⁰C and protect from light. Store in the outer carton.

After opening the oral solution can be used up to the expiration date on the bottle. The bottle and its contents should be discarded after the expiration date.

Medicine Classification: Prescription Only

Distributed by:

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New Zealand

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