

ENTECAVIR-TEVA

(Entecavir Tablets)

ENTECAVIR-TEVA FC TABLETS 0.5 MG

ENTECAVIR-TEVA FC TABLETS 1 MG

WARNING: SEVERE ACUTE EXACERBATIONS OF HEPATITIS B, PATIENTS CO- INFECTED WITH HIV AND HBV, and LACTIC ACIDOSIS AND HEPATOMEGALY

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 and Precautions** (4.1)].

Limited clinical experience suggests there is a potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if ENTECAVIR is used to treat chronic hepatitis B virus (HBV) infection in patients with HIV infection that is not being treated. Therapy with ENTECAVIR is not recommended for HIV/ HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART) [see **Warnings and Precautions** (4.2)].

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 [see **Warnings and Precautions** (4.3)].

1 INDICATIONS AND USAGE

Entecavir is indicated for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

The following points should be considered when initiating therapy with Entecavir:

This indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment-naïve and lamivudine-resistant adult subjects with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease [see *Clinical Studies* (1.2)].

- Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease [see *Adverse Reactions* (2)] and *Clinical Studies* (1.2,1.3).
- Virologic, biochemical, serologic, and safety data are available for a limited number of adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy [see *Warnings and Precautions* (4.2) and *Clinical Studies* (12.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Compensated Liver Disease

The recommended dose of Entecavir for chronic hepatitis B virus infection in nucleoside- treatment-naïve adults and adolescents 16 years of age and older is 0.5 mg once daily, with or without food.

The recommended dose of Entecavir 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).

Decompensated Liver Disease

The recommended dose of Entecavir for chronic hepatitis B virus infection in adults with decompensated liver disease 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).

2.2 Renal Impairment

In subjects with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased [see *Clinical Pharmacology* (10.2)]. Dosage adjustment is recommended for patients with creatinine clearance less than 50 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in Table 1. The once-daily dosing regimens are preferred.

| Table 1: Recommended Dosage of ENTECAVIR in Patients with Renal Impairment | | |
|--|-----------------------|---|
| Creatinine Clearance (mL/min) | Usual Dose (0.5 mg) | Lamivudine-Refractory or Decompensated Liver Disease (1 mg) |
| ≥50 | 0.5 mg once daily | 1 mg once daily |
| 30 to <50 | 0.5 mg every 48 hours | 0.5 mg once daily OR 1 mg every 48 hours |
| 10 to <30 | 0.5 mg every 72 hours | 1 mg every 72 hours |
| <10 Hemodialysis ^a or CAPD | 0.5 mg every 7 days | 1 mg every 7 days |

^a If administered on a hemodialysis day, administer Entecavir after the hemodialysis session.

2.3 Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

2.4 Duration of Therapy

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

3 CONTRAINDICATIONS

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

4 WARNINGS AND PRECAUTIONS

4.1 Severe Acute Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir [see *Adverse Reactions* (5.1)]. 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.

4.2 Patients Co-infected with HIV and HBV

Entecavir 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 Entecavir is used to treat chronic hepatitis B virus infection in patients with HIV infection that is not being treated [see *Microbiology* (10.3)]. Therefore, therapy with Entecavir is not recommended for HIV/HBV co-infected patients who are not also receiving HAART. Before initiating Entecavir therapy, HIV antibody testing should be offered to all patients. Entecavir has not been studied as a treatment for HIV infection and is not recommended for this use.

4.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including Entecavir, alone or in combination with antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors.

Lactic acidosis with Entecavir use has been reported, often in association with hepatic decompensation, other serious medical conditions, or drug exposures. Patients with decompensated liver disease may be at higher risk for lactic acidosis. Treatment with Entecavir should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

4.4 Patients with Decompensated Liver Disease

A higher rate of serious hepatic adverse events (regardless of causality) has been observed in patients with decompensated liver disease, in particular in those with Child-Turcotte-Pugh (CTP) class C disease, compared with rates in patients with compensated liver function. Also, patients with decompensated liver disease may be at higher risk for lactic acidosis and for specific renal adverse events such as hepatorenal syndrome. Therefore, clinical and laboratory parameters should be closely monitored in this patient population [see *Adverse Reactions* (5.1)].

4.5 Resistance and Specific Precaution for Lamivudine-Refractory Patients

Mutations in the HBV polymerase that encode lamivudine-resistance substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with entecavir associated resistance (ETVR). In a small percentage of lamivudine-refractory patients, ETVr substitutions at residues rt1894, rt2592 or rt2593 were present at baseline. Patients with lamivudine-resistant HBV are at higher risk of developing subsequent entecavir resistance than patients without lamivudine resistance. The cumulative probability of emerging genotypic entecavir resistance after 1, 2, 3, 4 and 5 years treatment in the lamivudine-refractory studies was 6%, 15%, 36%, 47% and 51%, respectively. Virological response should be frequently monitored in the lamivudine-refractory population and appropriate resistance testing should be performed. In patients with a suboptimal virological response after 24 weeks of treatment with entecavir, a modification of treatment should be considered.

Pre-existing lamivudine-resistant HBV is associated with an increased risk for subsequent entecavir resistance regardless of the degree of liver disease. In patients with decompensated liver disease, virologic breakthrough may be associated with serious clinical complications of the underlying liver disease. Therefore, in patients with both decompensated liver disease and lamivudine-resistant HBV, combination use of entecavir plus a second antiviral agent (which does not share cross-resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy [see *Clinical Pharmacology* (10.3)].

4.6 Excipient with known effect

Lactose: Entecavir tablets should be used with caution in patients with lactose intolerance [see *Description* (9)].

5 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

Exacerbations of hepatitis after discontinuation of treatment [see *Boxed Warning, Warnings and Precautions* (4.1)].

Lactic acidosis and severe hepatomegaly with steatosis [see *Boxed Warning, Warnings and Precautions* (4.3)].

5.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Compensated Liver Disease

Assessment of adverse reactions is based on four studies (A1463014, A1463022, A1463026, and A1463027) in which 1720 subjects with chronic hepatitis B virus infection and compensated liver disease received double-blind treatment with Entecavir 0.5 mg/day (n=679), Entecavir 1 mg/day (n=183), or lamivudine (n=858) for up to 2 years. Median duration of therapy was 69 weeks for Entecavir-treated subjects and 63 weeks for lamivudine-treated subjects in Studies A1463022 and A1463027 and 73 weeks for Entecavir-treated subjects and 51 weeks for lamivudine-treated subjects in Studies A1463026 and A1463014. The safety profiles of Entecavir and lamivudine were comparable in these studies. The most common adverse reactions of any severity (≥3%) with at least a possible relation to study drug for Entecavir-treated subjects were headache, fatigue, and dizziness. The most common adverse reactions among lamivudine-treated subjects were headache, fatigue, and dizziness. One percent of Entecavir-treated subjects in these four studies compared with 4% of lamivudine-treated subjects discontinued for adverse events or abnormal laboratory test results.

Clinical adverse reactions of moderate-severe intensity and considered at least possibly related to treatment occurring during therapy in four clinical studies in which Entecavir was compared with lamivudine are presented in Table 2.

| Table 2: Clinical Adverse Reactions ^a of Moderate-Severe Intensity (Grades 2-4) Reported in Four Entecavir Clinical Trials Through 2 Years | | | | |
|---|-------------------------------|---------------------------|------------------------------------|---------------------------|
| Body System/ Adverse Reaction | Nucleoside-Naïve ^b | | Lamivudine-Refractory ^c | |
| | ENTECAVIR 0.5mg n=679 | Lamivudine 100mg n=668 | ENTECAVIR 1mg n=183 | Lamivudine 100mg n=190 |
| Any Grade 2-4 adverse reaction ^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 A1463022 and A1463027.

^c Includes Study A1463026 and the Entecavir 1-mg and lamivudine treatment arms of Study A1463014, a Phase 2 multinational, randomized, double-blind study of three doses of Entecavir (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 Entecavir compared with lamivudine are listed in Table 3.

| Table 3: Selected Treatment-Emergent ^a Laboratory Abnormalities Reported in Four Entecavir Clinical Trials Through 2 Years | | | | |
|---|-------------------------------|------------------------------|------------------------------------|------------------------------|
| Test | Nucleoside-Naïve ^b | | Lamivudine-Refractory ^c | |
| | ENTECAVIR 0.5mg n=679 | Lamivudine 100mg n=668 | ENTECAVIR 1mg n=183 | Lamivudine 100mg 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% |
| Albumin <2.5 g/dL | <1% | <1% | 0 | 2% |
| Total bilirubin >2.5 X ULN | 2% | 2% | 3% | 2% |
| Ulipase ≥2.1 X ULN | 7% | 6% | 7% | 7% |
| Creatinine ≥3.0 X ULN | 0 | 0 | 0 | 0 |
| Confirmed creatinine increase ≥0.5 mg/dL | 1% | 1% | 2% | 1% |
| Hyperglycemia, fasting >250 mg/dL | 2% | 1% | 3% | 1% |
| Glycosuria ^e | 4% | 3% | 4% | 6% |
| Hematuria ^e | 9% | 10% | 9% | 6% |
| Platelets <50,000/mm ³ | <1% | <1% | <1% | <1% |

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

^b Studies A1463022 and A1463027.

^c Includes Study A1463026 and the BARACLUDE 1 mg and lamivudine treatment arms of Study A1463014, 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, ≥ 500 mg/dL; Grade 4 = 4+, marked, severe.

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

ULN = upper limit of normal

Among Entecavir-treated subjects in these studies, on-treatment ALT elevations greater than 10 times the upper limit of normal (ULN) and greater than 2 times 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

An exacerbation of hepatitis or ALT flare was defined as ALT greater than 10 times the upper limit of normal (ULN) and greater than 2 times 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 4 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 Entecavir is discontinued without regard to treatment response, the rate of post-treatment flares could be higher [see also *Warnings and Precautions* (4.1)].

| Table 4: Exacerbations of Hepatitis During Off-Treatment Follow-up, Subjects in Studies A1463022, A1463027, and A1463026 | | |
|--|-------------|--------------|
| Subjects with ALT Elevations >10 X ULN and >2 X Reference ^a | | |
| | Entecavir | Lamivudine |
| Nucleoside-naïve | | |
| 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 Entecavir-treated subjects and 10 weeks for lamivudine-treated subjects.

Decompensated Liver Disease

Study A1463048 was a randomized, open-label study of Entecavir 1mg once daily versus adefovir dipivoxil 10 mg once daily given for up to 48 weeks in adult subjects with chronic HBV infection and evidence of hepatic decompensation, defined as a Child-Turcotte-Pugh (CTP) score of 7 or higher [see *Clinical Studies* (12.1)]. Among the 102 subjects receiving Entecavir, the most common treatment-emergent adverse events of any severity, regardless of causality, occurring through Week 48 were peripheral edema (16%), ascites (15%), pyrexia (14%), hepatic encephalopathy (10%), and upper respiratory infection (10%). Clinical adverse reactions not listed in Table 2 that were observed through Week 48 include blood bicarbonate decreased (2%) and renal failure (<1%).

Eighteen of 102 (18%) subjects treated with Entecavir and 18/89 (20%) subjects treated with adefovir dipivoxil died during the first 48 weeks of therapy. The majority of deaths (11 in the Entecavir group and 16 in the adefovir dipivoxil group) were due to liver-related causes such as hepatic failure, hepatic encephalopathy, hepatorenal syndrome, and upper gastrointestinal hemorrhage. The rate of hepatocellular carcinoma (HCC) through Week 48 was 6% (6/102) for subjects treated with Entecavir and 8% (7/89) for subjects treated with adefovir dipivoxil. Five percent of subjects in either treatment arm discontinued therapy due to an adverse event through Week 48.

No subject in either treatment arm experienced an on-treatment hepatic flare (ALT >2 X baseline and >10 X ULN) through Week 48. Eleven of 102 (11%) subjects treated with Entecavir and 11/89 (13%) subjects treated with adefovir dipivoxil had a confirmed increase in serum creatinine of 0.5 mg/dL through Week 48.

HIV/HBV Co-infected

The safety profile of Entecavir 1 mg (n=51) in HIV/HBV co-infected subjects enrolled in Study A1463038 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 and Precautions* (4.2)].

Liver Transplant Recipients

Among 65 subjects receiving Entecavir in an open-label, post-liver transplant trial [see *Use in Specific Populations* (7.8)], the frequency and nature of adverse events were consistent with those expected in patients who have received a liver transplant and the known safety profile of Entecavir.

5.2 Postmarketing Experience

Data from Long-Term Observational Study

Study A1463080 was a randomized, global, observational, open-label Phase 4 study to assess long-term risks and benefits of Entecavir (0.5 mg/day or 1 mg/day) treatment as compared to other standard-of-care HBV nucleos(t)ide analogues in subjects with chronic HBV infection.

A total of 12,378 patients were treated with Entecavir (n=6,216) or other HBV nucleos(t)ide treatment (non-entecavir [ETV]) (n=6,162). Patients were evaluated at baseline and subsequently every 6 months for up to 10 years. The principal clinical outcome events assessed during the study were overall malignant neoplasms, liver-related HBV disease progression, HCC, non-HCC malignant neoplasms, and death. The study showed that Entecavir was not significantly associated with an increased risk of malignant neoplasms compared to other standard-of-care HBV nucleos(t)ides, as assessed by either the composite endpoint of overall malignant neoplasms or the individual endpoint of non-HCC malignant neoplasms. The most commonly reported malignancy in both the Entecavir and non-ETV groups was HCC, followed by gastrointestinal malignancies. The data also showed that long-term Entecavir use was not associated with a lower occurrence of HBV disease progression or a lower rate of death overall compared to other HBV nucleos(t)ides. The principal clinical outcome event assessments are shown in Table 5.

| Table 5: Principal Analyses of Time to Adjudicated Events - Randomized Treated Subjects | | | |
|---|--------------------------------|--------------------|--|
| Endpoint ^c | Number of Subjects with Events | | Hazard Ratio [ENTECAVIR-Non-ETV] (CI) ^b |
| | ENTECAVIR N=6,216 | Non-ETV N=6,162 | |
| Primary Endpoints | | | |
| Overall malignant neoplasm | 331 | 337 | 0.93 (0.800, 1.084) |
| Liver-related HBV disease progression | 350 | 375 | 0.89 (0.769, 1.030) |
| Death | 238 | 264 | 0.85 (0.713, 1.012) |
| Secondary Endpoints | | | |
| Non-HCC malignant neoplasm | 95 | 81 | 1.10 (0.817, 1.478) |
| HCC | 240 ^b | 263 | 0.87 (0.727, 1.032) |

Analyses were stratified by geographic region and prior HBV nucleos(t)ide experience.

^a 95.03% CI for overall malignant neoplasm, death, and liver-related HBV disease progression; 95% CI for non- HCC malignant neoplasm and HCC.

^b One subject had a pre-treatment HCC event and was excluded from the analysis.

^c Overall malignant neoplasm is a composite event of HCC or non-HCC malignant neoplasm. Liver-related HBV disease progression is a composite event of liver-related death, HCC, or non-HCC HBV disease progression. CI = confidence interval; N = total number of subjects.

Limitations of the study included potential outcome changes over the long-term follow-up period and more frequent post-randomization treatment changes in the non-ETV group. In addition, the study was underpowered to demonstrate a difference in the non-HCC malignancy rate because of the lower than expected background rate.

Adverse Reactions from Postmarketing Spontaneous Reports

The following adverse reactions have been reported during postmarketing use of Entecavir. Because these reactions were reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to Entecavir exposure.

Immune system disorders: anaphylactoid reaction.

Metabolism and nutrition disorders: lactic acidosis.

Hepatobiliary disorders: increased transaminases.

Skin and subcutaneous tissue disorders: alopecia, rash.

6 DRUG INTERACTIONS

Since entecavir is primarily eliminated by the kidneys [see *Clinical Pharmacology* (10.2)], coadministration of Entecavir 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 Entecavir 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 Entecavir is coadministered with such drugs.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Entecavir in pregnant women. When pregnant rats and rabbits received entecavir at 28 and 212 times the human exposure at the highest human dose, there were no signs of embryofetal toxicity. Because animal reproduction studies are not always predictive of human response, Entecavir should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits.

Developmental toxicity studies were performed in rats and rabbits. There were no signs of embryofetal or maternal toxicity when pregnant animals received oral entecavir at approximately 28 (rat) and 212 (rabbit) times the human exposure achieved at the highest recommended human dose of 1 mg/day. In rats, maternal toxicity, embryofetal toxicity (resorptions), lower fetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternbrae, and phalanges), and extra lumbar vertebrae and ribs were observed at exposures 31.00 times those in humans. In rabbits, embryofetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th ribs were observed at exposures 883 times those in humans. In a peri-postnatal study, no adverse effects on offspring occurred when rats received oral entecavir at exposures greater than 94 times those in humans.

7.2 Labor and Delivery

There are no studies in pregnant women and 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.

7.3 Nursing Mothers

It is not known whether Entecavir is excreted into human milk; however, entecavir is excreted into the milk of rats. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from Entecavir, a decision should be made to discontinue nursing or to discontinue Entecavir taking into consideration the importance of continued hepatitis B therapy to the mother and the known benefits of breastfeeding.

7.4 Pediatric Use

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

7.5 Geriatric Use

Clinical studies of Entecavir 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* (2.2)].

7.6 Racial/Ethnic Groups

There are no significant racial differences in entecavir pharmacokinetics. The safety and efficacy of Entecavir 0.5 mg once daily were assessed in a single-arm, open-label trial of HBeAg-positive or -negative, nucleoside-naïve, Black/African American (n=40) and Hispanic (n=6) subjects with chronic HBV infection. In this trial, 76% of subjects were male, the mean age was 42 years, 5.7% were HBeAg-positive, the mean baseline HBV DNA was 7.0 log₁₀ IU/mL, and the mean baseline ALT was 162 U/L. At Week 48 of treatment, 32 of 46 (70%) subjects had HBV DNA <50 IU/mL (approximately 300 copies/mL), 31 of 46 (67%) subjects had ALT normalization (≤1 × ULN), and 12 of 26 (46%) HBeAg-positive subjects had HBe seroconversion. Safety data were similar to those observed in the larger controlled clinical trials.

Because of low enrollment, safety and efficacy have not been established in the US Hispanic population.

7.7 Renal Impairment

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% faster 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 Entecavir should be based on the renal function of the patient, rather than age [see *Dosage and Administration* (2.2)].

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 virus 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 5 [see *Dosage and Administration* (2.2)].

Table 5: 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* 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) |
| CL _R (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) |

* Dosed immediately following hemodialysis.

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

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 [see *Dosage and Administration* (2.2)].

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

Post-liver transplant: Limited data are available on the safety and efficacy of Entecavir in liver transplant recipients. 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 [see *Use in Specific Populations* (7.8)].

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, 2B6, 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. 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 [see *Drug Interactions* (6)].

10.3 Microbiology

Mechanism of Action

Entecavir, a guanosine nucleoside analogue with activity against HBV reverse transcriptase (RT), 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 reverse transcriptase: (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, β, 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, EC₅₀) at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. The median EC₅₀ value for entecavir against lamivudine-resistant HBV (rtL180M, rtM204V) was 0.026 μM (range 0.010-0.059 μM).

The coadministration of HBV nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) with Entecavir is unlikely to reduce the antiviral efficacy of Entecavir 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 or emtricitabine at concentrations greater than 100 times the C_{max} of entecavir using the 1-mg dose.

Antiviral Activity against HIV

A comprehensive analysis of the inhibitory activity of entecavir against a panel of laboratory and clinical HIV type 1 (HIV-1) isolates using a variety of cells and assay conditions yielded EC₅₀ values ranging from 0.026 to >10 μM; the lower EC₅₀ 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 rtM204V/I with or without 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 reverse transcriptase. Lamivudine-resistant strains harboring rtL180M plus rtM204V in combination with the amino acid substitution rtA181C conferred 16- to 122-fold reductions in entecavir phenotypic susceptibility.

In Clinical Studies

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

Nucleoside-naïve subjects: Through Week 240 in nucleoside-naïve studies, genotypic evidence of entecavir resistance-associated (ETV) substitutions at rtT184, rtS202, or rtM250 was identified in 3 subjects treated with entecavir, 2 of whom experienced virologic breakthrough (see Table 6). These substitutions were observed only in the presence of lamivudine resistance-associated (LVD) substitutions (rtM204V and rtL180M).

| Table 6: Emerging Genotypic Entecavir Resistance Through Year 5, Nucleoside-Naïve Studies | | | | | |
|---|--------|--------|---------------------|---------------------|---------------------|
| | Year 1 | Year 2 | Year 3 ^a | Year 4 ^a | Year 5 ^a |
| Subjects treated and monitored for resistance ^b | 663 | 278 | 149 | 121 | 108 |
| Subjects in specific year with: | | | | | |
| - emerging genotypic ETV ^{c,d} | 1 | 1 | 1 | 0 | 0 |
| - genotypic ETV ^{c,d} with virologic breakthrough ^e | 1 | 0 | 1 | 0 | 0 |
| Cumulative probability of: | | | | | |
| - emerging genotypic ETV ^{c,d} | 0.2% | 0.5% | 1.2% | 1.2% | 1.2% |
| - genotypic ETV ^{c,d} with virologic breakthrough ^e | 0.2% | 0.2% | 0.8% | 0.8% | 0.8% |

- ^a Results reflect use of a 1-mg dose of entecavir for 147 of 149 subjects in Year 3 and all subjects in Years 4 and 5 and of combination entecavir-lamivudine therapy (followed by long-term entecavir therapy) for a median of 20 weeks for 130 of 149 subjects in Year 3 and for 1 week for 1 of 121 subjects in Year 4 in a rollover study.
- ^b Includes subjects with at least one on-therapy HBV DNA measurement by PCR at or after Week 24 through week 58 (Year 1), after week 58 through week 102 (Year 2), or after week 102 through week 156 (Year 3), after week 156 through week 204 (Year 4), or after week 204 through week 252 (Year 5).
- ^c ETV = entecavir resistance substitutions at residues rtT184, rtS202, or rtM250.
- ^d Patients also had lamivudine resistance substitutions (rtM204V and rtL180M).
- ^e ≥1 log₁₀ increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point.

Lamivudine-refractory subjects: ETV substitutions (in addition to LVD substitutions rtM204V/I ± rtL180M) were observed at baseline in isolates from 10/187 (5%) lamivudine-refractory subjects 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 the 10 subjects experienced virologic breakthrough (≥1 log₁₀ increase above nadir). Emerging entecavir resistance in lamivudine-refractory studies through Week 240 is summarized in Table 7.

| Table 7: Emerging Genotypic Entecavir Resistance Through Year 5, Lamivudine-Refractory Studies | | | | | |
|--|-------------------|--------------------|---------------------|---------------------|---------------------|
| | Year 1 | Year 2 | Year 3 ^a | Year 4 ^a | Year 5 ^a |
| Subjects treated and monitored for resistance ^b | 187 | 146 | 80 | 52 | 33 |
| Subjects in specific year with: | | | | | |
| - emerging genotypic ETV ^{c,d} | 11 | 12 | 15 | 6 | 2 |
| - genotypic ETV ^{c,d} with virologic breakthrough ^e | 2 ^f | 14 ^f | 13 ^f | 9 ^f | 1 ^f |
| Cumulative probability of: | | | | | |
| - emerging genotypic ETV ^{c,d} | 6.2% | 15% | 36.3% | 46.6% | 54.45% |
| - genotypic ETV ^{c,d} with virologic breakthrough ^e | 1.1% ^f | 10.7% ^f | 27% ^f | 41.3% ^f | 43.6% ^f |

- ^a Results reflect use of combination entecavir-lamivudine therapy (followed by long-term entecavir therapy) for a median of 13 weeks for 48 of 80 subjects in Year 3, a median of 38 weeks for 10 of 52 subjects in Year 4, and for 16 weeks for 1 of 33 subjects in Year 5 in a rollover study.
- ^b Includes subjects with at least one on-therapy HBV DNA measurement by PCR at or after Week 24 through week 58 (Year 1), after week 58 through week 102 (Year 2), or after week 102 through week 156 (Year 3), after week 156 through week 204 (Year 4), or after week 204 through week 252 (Year 5).
- ^c ETV = entecavir resistance substitutions at residues rtT184, rtS202, or rtM250.
- ^d Patients also had lamivudine resistance substitutions (rtM204V/I ± rtL180M).
- ^e ≥1 log₁₀ increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point.
- ^f ETV occurring in any year; virologic breakthrough in specified year.

Among lamivudine-refractory subjects with baseline HBV DNA <10⁷ log₁₀ copies/mL, 64% (9/14) achieved HBV DNA <300 copies/mL at Week 48. These 14 subjects had a lower rate of genotypic entecavir resistance (cumulative probability 18.8% through 5 years of follow-up) than the overall study population (see Table 7). Also, lamivudine-refractory subjects who achieved HBV DNA <10⁷ log₁₀ copies/mL by PCR at Week 24 had a lower rate of resistance than those who did not (5-year cumulative probability 17.6% [n=50] versus 60.5% [n=135], respectively).

In a post-approval integrated analysis of entecavir resistance data from 17 Phase 2 and 3 clinical trials, an emergent entecavir resistance-associated substitution rtA181C was detected in 5 out of 1461 (0.3%) subjects during treatment with entecavir. This substitution was detected only in the presence of lamivudine resistance-associated substitutions rtL180M plus rtM204V.

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 (rtM204V/I with or without rtL180M than for wild-type HBV. Substitutions rtM204V/I with or without rtL180M or rtL173L, which are associated with lamivudine and telbivudine resistance, also confer decreased phenotypic susceptibility to entecavir. 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. Recombinant HBV genomes encoding adefovir resistance-associated substitutions at either nt236T or ntA181V had 0.3- and 1.1-fold shifts in susceptibility to entecavir in cell culture, respectively.

11 NONCLINICAL TOXICOLOGY

11.1 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 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 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 greater than 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 35 times or greater than those achieved in humans. No testicular changes were evident in monkeys.

12 CLINICAL STUDIES

The safety and efficacy of Entecavir were evaluated in three Phase 3 active-controlled trials [see *Clinical Studies* (12.1), (12.2)]. These studies included 1633 subjects 16 years of age or older with chronic hepatitis B virus infection (serum HBeAg-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 at least 1.3 times ULN and chronic inflammation on liver biopsy compatible with a diagnosis of chronic viral hepatitis. The safety and efficacy of Entecavir were also evaluated in a study of 191 HBV-infected subjects with decompensated liver disease and in a study of 68 subjects co-infected with HBV and HIV [see *Clinical Studies* (12.1)].

12.1 Outcomes at 48 Weeks

Nucleoside-naïve Subjects with Compensated Liver Disease

HBeAg-positive: Study AI463022 was a multinational, randomized, double-blind study of Entecavir 0.5 mg once daily versus lamivudine 100 mg once daily for a minimum of 52 weeks in 709 (of 715 randomized) nucleoside-naïve subjects with chronic hepatitis B virus infection, compensated liver disease 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-α. 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 log₁₀ 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 Entecavir 0.5 mg once daily versus lamivudine 100 mg once daily for a minimum of 52 weeks in 638 (of 648 randomized) nucleoside-naïve subjects with HBeAg-negative (HBeAb-positive) chronic hepatitis B virus infection and compensated liver disease. The mean age of subjects was 44 years, 76% were male, 39% were Asian, 58% were Caucasian, and 13% had previously received interferon-α. 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 log₁₀ 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, Entecavir was superior to lamivudine on the primary efficacy endpoint of Histologic Improvement, defined as a 2-point or greater 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 8. Selected virologic, biochemical, and serologic outcome measures are shown in Table 9.

| | Study AI463022 (HBeAg-Positive) | | Study AI463027 (HBeAg-Negative) | |
|--|---|--|---|--|
| | ENTECAVIR 0.5 mg n=314 ^a | Lamivudine 100 mg n=314 ^a | ENTECAVIR 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 ^d | 8% | 10% | 12% | 15% |
| Missing Week 48 biopsy | 7% | 14% | 10% | 13% |

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

Table 9: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Nucleoside-Naïve Subjects in Studies AI463022 and AI463027

| | Study AI463022 (HBeAg-Positive) | | Study AI463027 (HBeAg-Negative) | |
|---|------------------------------------|-------------------------------|------------------------------------|-------------------------------|
| | ENTECAVIR 0.5 mg n=354 | Lamivudine 100 mg n=355 | ENTECAVIR 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 [lower limit of quantification (LLOQ) = 300 copies/mL].

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

Lamivudine-refractory Subjects with Compensated Liver Disease

Study AI463026 was a multinational, randomized, double-blind study of Entecavir in 286 (of 293 randomized) subjects with lamivudine-refractory chronic hepatitis B virus infection and compensated liver disease. Subjects receiving lamivudine at study entry either switched to Entecavir 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, 78% were male, 37% were Asian, 52% were Caucasian, and 52% had previously received interferon-α. The mean duration of prior lamivudine therapy was 2.7 years, and 85% had lamivudine resistance mutations at baseline by an investigational line probe assay. At baseline, 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 log₁₀ copies/mL, and mean serum ALT level was 128 U/L. Paired, adequate liver biopsy samples were available for 87% of subjects.

Entecavir 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 10. Table 11 shows selected virologic, biochemical, and serologic endpoints.

Table 10: Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Lamivudine-Refractory Subjects in Study AI463026

| | ENTECAVIR 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 ≥2).

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

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

Table 11: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Lamivudine-Refractory Subjects in Study AI463026

| | ENTECAVIR 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).

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

Subjects with Decompensated Liver Disease

Study AI463048 was a randomized, open-label study of Entecavir 1 mg once daily versus adefovir dipivoxil 10 mg once daily in 191 (of 195 randomized) adult subjects with HBeAg-positive or -negative chronic HBV infection and evidence of hepatic decompensation, defined as a Child-Turcotte-Pugh (CTP) score of 7 or higher. Subjects were either HBV-treatment-naïve or previously treated, predominantly with lamivudine or interferon-α.

In Study AI463048, 100 subjects were randomized to treatment with Entecavir and 91 subjects to treatment with adefovir dipivoxil. Two subjects randomized to treatment with adefovir dipivoxil actually received treatment with Entecavir for the duration of the study. The mean age of subjects was 52 years, 74% were male, 54% were Asian, 33% were Caucasian, and 5% were Black/African American. At baseline, subjects had a mean serum HBV DNA by PCR of 7.83 log₁₀ copies/mL and mean ALT level of 100 U/L; 54% of subjects were HBeAg-positive; 35% had genotypic evidence of lamivudine resistance. The baseline mean CTP score was 8.6. Results for selected study endpoints at Week 48 are shown in Table 12.

Table 12: Selected Endpoints at Week 48, Subjects with Decompensated Liver Disease, Study AI463048

| | ENTECAVIR 1 mg n=100 ^a | Adefovir Dipivoxil 10 mg n=91 ^a |
|--|---|--|
| HBV DNA ^b | | |
| Proportion undetectable (<300 copies/mL) | 57% | 20% |
| Stable or improved CTP score ^c | 61% | 67% |
| HBeAg loss | 5% | 0 |
| Normalization of ALT (≤1 X ULN) ^d | 49/78 (63%) | 33/71 (46%) |

^a Endpoints were analyzed using intention-to-treat (ITT) method, treated subjects as randomized.

^b Roche COBAS AmpliCor PCR assay (LLOQ = 300 copies/mL).

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