Rx Prescription only

Entecavir STELLA 0.5 mg film-coated tablet

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 *Special warning and precautions for use (8a)*].

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 *Special warning and precautions for use (8b)*].

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 *Special warning and precautions for use (8c)*].

1. Name of the medicinal product

Entecavir STELLA 0.5 mg film-coated tablet

2. Special notice and recommendation

Keep out of reach of children

Read the package insert carefully before use

3. Composition

Each film-coated tablet contains:

Entecavir (as entecavir monohydrate) ..... 0.5 mg

Excipients:

Calcium carbonate, pregelatinized starch, soy polysaccharides, carmellose sodium, anhydrous citric acid, sodium stearyl fumarate, hypromellose, titanium dioxide, macrogol, polysorbate 80.

4. Pharmaceutical form

Film-coated tablet.

White, triangle-shaped, film-coated tablet, engraved with “0.5” on one side and “E” on the other side.

5. Indications

Entecavir STELLA 0.5 mg film-coated tablet 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*].
- 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 and Clinical studies*].
- 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 *Special warnings and precautions for use and Clinical studies*].

6. Administration and dosage

Administration

Entecavir STELLA 0.5 mg film-coated tablet should be taken orally.

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).

Special population

- *Patients with renal impairment*

In subjects with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased. 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 STELLA 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	0.5 mg every 7 days	1 mg every 7 days
Hemodialysis* or CAPD	0.5mg every 7 days	1 mg every 7 days

Do not split tablets.

* If administered on a hemodialysis day, administer entecavir after the hemodialysis session.

CAPD = continuous ambulatory peritoneal dialysis

- *Patients with hepatic impairment*

No dosage adjustment is required in patients with hepatic impairment.

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.

7. Contraindications

Hypersensitivity to the active substance or to any of the excipients of the product.

8. Special warnings and precautions for use

(a) 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. 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.

(b) 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 of 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. 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.

(c) 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).

(d) 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.

(e) Resistance and specific precaution for lamivudine-refractory patients:

Mutations in the HBV polymerase that encode lamivudine-resistance substitutions may lead to the subsequent emergency of secondary substitutions, including those associated with entecavir associated resistance (ETVr). In a small percentage of lamivudine-refractory patients, ETVr substitutions at residues rtT184, rtS202 or rtM250 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.

(f) Pediatric Use

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

(g) 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.

(h) 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, 57% were HBeAg-positive, the mean baseline HBV DNA was 7.0 $\log_{10}$ 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 x 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.

(i) Renal Impairment

Dosage adjustment of entecavir is recommended for patients with creatinine clearance less than 50 mL/min, including patients on hemodialysis or CAPD.

(j) Liver Transplant Recipients

The safety and efficacy of entecavir were assessed in a single-arm, open-label trial in 65 subjects who received a liver transplant for complications of chronic HBV infection. Eligible subjects who had HBV DNA less than 172 IU/mL (approximately 1000 copies/mL) at the time of transplant were treated with entecavir 1 mg once daily in addition to usual post-transplantation management, including hepatitis B immune globulin. The trial population was 82% male, 39% Caucasian, and 37% Asian, with a mean age of 49 years; 89% of subjects had HBeAg-negative disease at the time of transplant.

Four of the 65 subjects received 4 weeks or less of entecavir (2 deaths, 1 retransplantation, and 1 protocol violation) and were not considered evaluable. Of the 61 subjects who received more than 4 weeks of entecavir, 60 received hepatitis B immune globulin post-transplant. Fifty-three subjects (82% of all 65 subjects treated) completed the trial and had HBV DNA measurements at or after 72 weeks treatment post-transplant. All 53 subjects had HBV DNA <50 IU/mL (approximately 300 copies/mL). Eight evaluable subjects did not have HBV DNA data available at 72 weeks, including 3 subjects who died prior to study completion. No subjects had HBV DNA values ≥50 IU/mL while receiving entecavir (plus hepatitis B immune globulin). All 61 evaluable subjects lost HBsAg post-transplant; 2 of these subjects experienced recurrence of measurable HBsAg without recurrence of HBV viremia. This trial was not designed to determine whether addition of entecavir to hepatitis B immune globulin

decreased the proportion of subjects with measurable HBV DNA post-transplant compared to hepatitis B immune globulin alone.

If entecavir treatment is determined to be necessary for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus, renal function must be carefully monitored both before and during treatment with entecavir.

9. Pregnancy and lactation

Pregnancy

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, sternebrae, and phalanges), and extra lumber vertebrae and ribs were observed at exposures 3100 times those in humans. In rabbits, embryofetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed at exposures 883 times those in humans. In a peri-postnatal study, no adverse effects on offspring occurred when rats received oral entecavir at exposures greater than 94 times those in humans.

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.

Lactation

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.

10. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Dizziness, fatigue and somnolence are common side effects which may impair the ability to drive and use machines.

11. Interactions with other drugs

Since entecavir is primarily eliminated by the kidneys, 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.

12. Adverse reactions

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 (AI463014, AI463022, AI463026, and AI463027) 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 AI463022 and AI463027 and 73 weeks for entecavir-treated subjects and 51 weeks for lamivudine-treated subjects in Studies AI463026 and AI463014. 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, dizziness, and nausea. 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

	Nucleoside-Naïve[b]		Lamivudine-Refractory[c]	
Body System/ Adverse Reaction	**Entecavir 0.5 mg n=679**	**Lamivudine 100 mg n=668**	**Entecavir 1 mg n=183**	**Lamivudine 100 mg 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 AI463022 and AI463027.

[c] Includes Study AI463026 and the entecavir 1-mg and lamivudine treatment arms of Study AI463014, 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 test 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

	Nucleoside-Naïve[b]		Lamivudine-Refractory[c]	
Test	**Entecavir 0.5 mg n=679**	**Lamivudine 100 mg n=668**	**Entecavir 1 mg n=183**	**Lamivudine 100 mg n=190**
Any Grade 3-4 laboratory abnormality[d]	35%	36%	37%	45%
ALT >10 X ULN and >2 X baseline	2%	4%	2%	11%
ALT >5.0 X ULN	11%	16%	12%	24%
Albumin <2.5 g/dL	<1%	<1%	0	2%
Total bilirubin >2.5 X ULN	2%	2%	3%	2%
Lipase ≥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[f]	9%	10%	9%	6%
Platelets <50,000/mm^3	<1%	<1%	<1%	<1%

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

[b] Studies AI463022 and AI463027.

[c] Includes Study AI463026 and the entecavir 1 mg and lamivudine treatment arms of Study AI463014, 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.

[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 $\log_{10}$/mL reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations of hepatitis after discontinuation of treatment

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.

Table 4: Exacerbations of Hepatitis During Off-Treatment Follow-up, Subjects in Studies AI463022, AI463027, and AI463026

	Subjects with ALT Elevations >10 X ULN and >2 X Reference[a]	
	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 AI463048 was a randomized, open-label study of entecavir 1 mg 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. 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 AI463038 was similar to that of placebo (n=17) through 24 weeks of blinded treatment and similar to that seen in non-HIV infected subjects.

Liver Transplant Recipients

Among 65 subjects receiving entecavir in an open-label, post-liver transplant trial, 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.

Postmarketing Experience

Data from Long-Term Observational Study

Study AI463080 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

	Number of Subjects with Events		
Endpoint[c]	**Entecavir N=6,216**	**Non-ETV N=6,162**	**Hazard Ratio [Entecavir: Non-ETV] (CI[a])**
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 population 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: rash, alopecia

13. Overdosage and management

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.

14. Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors.

ATC code: J05AF10.

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 Ki values ranging from 18 to >160 μM.

Antiviral activity

Entecavir inhibited HBV DNA synthesis (50% reduction, EC_{50}) at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. The median EC_{50} value for entecavir against lamivudine-resistant HBV (rtL180M, rtM204V) was 0.026 μM (range 0.010-0.059 μM).

The coadministration of HIV nucleoside/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 EC_{50} values ranging from 0.026 to >10 μM; the lower EC_{50} values were observed when decreased levels of virus were used in the assay. In cell culture, entecavir selected for an M184I substitution in HIV reverse transcriptase at micromolar concentrations, confirming inhibitory pressure at high entecavir concentrations. HIV variants containing the M184V substitution showed loss of susceptibility to entecavir.

Resistance in cell culture

In cell-based assays, 8- to 30-fold reductions in entecavir phenotypic susceptibility were observed for lamivudine-resistant strains. Further reductions (>70-fold) in entecavir phenotypic susceptibility required the presence of amino acid substitutions rtM204I/V 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.

Resistance in clinical studies

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

Nucleoside-naïve subjects:

Through Week 240 in nucleoside-naïve studies, genotypic evidence of entecavir resistance-associated (ETVr) 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 (LVDr) 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 ETVr[c,d]	1	1	1	0	0
- genotypic ETVr[c,d] with virologic breakthrough[e]	1	0	1	0	0
Cumulative probability of:					
- emerging genotypic ETVr[c,d]	0.2%	0.5%	1.2%	1.2%	1.2%
- genotypic ETVr[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] ETVr = entecavir resistance substitutions at residues rtT184, rtS202, or rtM250.

[d] Patients also had lamivudine resistance substitutions (rtM204V and rtL180M).

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

Lamivudine-refractory subjects:

ETVr substitutions (in addition to LVDr 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 $\log_{10}$ 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 ETVr[c,d]	11	12	15	6	2
- genotypic ETVr[c,d] with virologic breakthrough[e]	2[f]	14[f]	13[f]	9[f]	1[f]
Cumulative probability of:					
- emerging genotypic ETVr[c,d]	6.2%	15%	36.3%	46.6%	54.45%
- genotypic ETVr[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] ETVr = entecavir resistance substitutions at residues rtT184, rtS202, or rtM250.

[d] Patients also had lamivudine resistance substitutions (rtM204V/I ± rtL180M).

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

[f] ETVr occurring in any year; virologic breakthrough in specified year.

Among lamivudine-refractory subjects with baseline HBV DNA $<10^7$ $\log_{10}$ 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 $<10^4$ $\log_{10}$ 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 rtM204I/V with or without rtL180M than for wild-type HBV. Substitutions rtM204I/V with or without rtL180M, rtL80I/V, or rtV173L, 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 rtN236T or rtA181V had 0.3- and 1.1-fold shifts in susceptibility to entecavir in cell culture, respectively.

15. Pharmacokinetic properties

Absorption

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

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

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

Distribution

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

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

Metabolism and elimination

Following administration of ^{14}C-entecavir in humans and rats, no oxidative or acetylated metabolites were observed. Minor amounts of phase II metabolites (glucuronide and sulfate conjugates) were observed. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system.

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

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

Special populations

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

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

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

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 8.

Table 8: Pharmacokinetic parameters in subjects with selected degrees of renal function						
	Renal function group					
	Baseline Creatinine Clearance (ml/min)					
	Unimpaired >80 (n = 6)	**Mild >50-≤80** (n = 6)	**Moderate 30-50** (n = 6)	**Severe <30** (n = 6)	**Severe Managed with Hemodialysis[a]** (n = 6)	**Severe managed with CAPD** (n = 4)
C_{max} (ng/ml) (CV%)	8.1 (30.7)	10.4 (37.2)	10.5 (22.7)	15.3 (33.8)	15.4 (56.4)	16.6 (29.7)
AUC(0-T) (ng·h /ml) (CV)	27.9 (25.6)	51.5 (22.8)	69.5 (22.7)	145.7 (31.5)	233.9 (28.4)	221.8 (11.6)
CLR (ml/min) (SD)	383.2 (101.8)	197.9 (78.1)	135.6 (31.6)	40.3 (10.1)	NA	NA
CLT/F (ml/min) (SD)	588.1 (153.7)	309.2 (62.6)	226.3 (60.1)	100.6 (29.1)	50.6 (16.5)	35.7 (19.6)

[a] Dosed immediately following hemodialysis.

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

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.

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.

Drug interactions

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

16. Nonclinical toxicology

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. It is not known how predictive the results of rodent carcinogenicity studies may be for humans [see *Postmarketing experience].*

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

adenomas were increased in females at exposures 24 times those in humans; combined adenomas and carcinomas were also increased in females at exposures 24 times those in humans. Brain gliomas were induced in both males and females at exposures 35 and 24 times those in humans. Skin fibromas were induced in females at exposures 4 times those in humans.

Entecavir was clastogenic to human lymphocyte cultures. Entecavir was not mutagenic in the Ames bacterial reverse mutations assay using *S. typhimurium and E. coli* strains in the presence or absence of metabolic activation, a mammalian-cell gene mutation assay, and a transformation assay with Syrian hamster embryo cells. Entecavir was also negative in an oral micronucleus study and an oral DNA repair study in rats. In reproductive toxicology studies, in which animals were administered entecavir at up to 30 mg/kg for up to 4 weeks, no evidence of impaired fertility was seen in male or female rats at systemic exposures 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.

17. Clinical studies

The safety and efficacy of entecavir were evaluated in three Phase 3 active-controlled trials [see below]. These studies included 1633 subjects 16 years of age or older with chronic hepatitis B virus infection (serum HBsAg-positive for at least 6 months) accompanied by evidence of viral replication (detectable serum HBV DNA, as measured by the bDNA hybridization or PCR assay). Subjects had persistently elevated ALT levels 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 below).

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 $\log_{10}$ copies/mL, and mean serum ALT level was 143 U/L. Paired, adequate liver biopsy samples were available for 89% of subjects.

HBeAg-negative (anti-HBe-positive/HBV DNA-positive): Study AI463027 was a multinational, randomized, double-blind study of 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 $\log_{10}$ copies/mL, and mean serum ALT level was 142 U/L. Paired, adequate liver biopsy samples were available for 88% of subjects.

In Studies AI463022 and AI463027, 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 9. Selected virologic, biochemical, and serologic outcome measures are shown in Table 10.

Table 9: Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Nucleoside Naïve Subjects in Studies AI463022 and AI463027

	HBeAg Positive (Study AI463022)		HBeAg Negative (Study AI463027)	
	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]
Histological improvement (Knodell Scores)				
Improvement[b]	72%	62%	70%	61%
No improvement	21%	24%	19%	26%
Ishak Fibrosis Score				
Improvement[c]	39%	35%	36%	38%
No change	46%	40%	41%	34%
Worsening[c]	8%	10%	12%	15%
Missing Week 48 biopsy	7%	14%	10%	13%

[a] Subjects with evaluable baseline histology (baseline Knodell Necroinflammatory Score ≥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 10: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Nucleoside-Naïve Subjects in Studies AI463022 and AI463027

	HBeAg Positive (Study AI463022)		HBeAg Negative (Study AI463027)	
	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, 76% were male, 37% were Asian, 62% were Caucasian, and 52% had previously received interferon-α. The mean duration of prior lamivudine therapy was 2.7 years, and 85% had lamivudine resistance mutations at baseline by an investigational line probe assay. At baseline, subjects had a mean Knodell Necroinflammatory Score of 6.5, mean serum HBV DNA as measured by Roche COBAS Amplicor PCR assay was 9.36 log_{10} copies/mL, and mean serum ALT level was 128 U/L. Paired, adequate liver biopsy samples were available for 87% of subjects.

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

Table 11: 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 12: Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Lamivudine Refractory Subjects in Studies 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 [lower limit of quantification (LLOQ) = 300 copies/mL].

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

Patients 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 log_{10} 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 13.

Table 13: 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%
HBsAg 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.

[d] Denominator is subjects with abnormal values at baseline.

ULN=upper limit of normal.

Subjects co-infected with HIV and HBV

Study AI463038 was a randomized, double-blind, placebo-controlled study of entecavir versus placebo in 68 subjects co-infected with HIV and HBV who experienced recurrence of HBV viremia while receiving a lamivudine-containing highly active antiretroviral (HAART) regimen. Subjects continued their lamivudine-containing HAART regimen (lamivudine dose 300 mg/day) and were assigned to add either entecavir 1 mg once daily (51 subjects) or placebo (17 subjects) for 24 weeks followed by an open-label phase for an additional 24 weeks where all subjects received entecavir. At baseline, subjects had a mean serum HBV DNA level by PCR of 9.13 log_{10} copies/mL. Ninety-nine percent of subjects were HBeAg-positive at baseline, with a mean baseline ALT level of 71.5 U/L. Median HIV RNA level remained stable at approximately 2 log_{10} copies/mL through 24 weeks of blinded therapy. Virologic and biochemical endpoints at Week 24 are shown in Table 14. There are no data in patients with HIV/HBV co-infection who have not received prior lamivudine therapy. entecavir has not been evaluated in HIV/HBV co-infected patients who were not simultaneously receiving effective HIV treatment.

Table 14: Virologic and Biochemical Endpoints at Week 24, Study AI463038		
	Entecavir 1 mg[a] n=51	Placebo[a] n=17
HBV DNA [b]		
Proportion undetectable (<300 copies/ml)	6%	0
Mean change from baseline (log_{10} copies/mL)	-3.65	+0.11
ALT normalization (≤1 X ULN)	34%[c]	8%[c]

[a] All subjects also received a lamivudine-containing HAART regimen.

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

[c] Percentage of subjects with abnormal ALT (>1 X ULN) at baseline who achieved ALT normalization (n=35 for entecavir and n=12 for placebo).

For subjects originally assigned to entecavir, at the end of the open-label phase (Week 48), 8% of subjects had HBV DNA <300 copies/mL by PCR, the mean change from baseline HBV DNA by PCR was -4.20 log_{10} copies/mL, and 37% of subjects with abnormal ALT at baseline had ALT normalization (≤1 X ULN).

Outcomes beyond 48 Weeks

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

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

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

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

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

Liver biopsy results: 57 subjects from the pivotal nucleoside-naïve Studies AI463022 (HBeAg- positive) and AI463027 (HBeAg-negative) who enrolled in a long-term rollover study were evaluated for long-term liver histology outcomes. The entecavir dosage was 0.5 mg daily in the pivotal studies (mean exposure 85 weeks) and 1 mg daily in the rollover study (mean exposure 177 weeks), and 51 subjects in the rollover study initially also received lamivudine (median duration 29 weeks). Of these subjects 55 (96%) had histological improvement as previously defined (see Table 10, footnote b), and 50 (88%) had a ≥1-point decrease in Ishak fibrosis score. For the 43 subjects with baseline Ishak Fibrosis Score ≥2, 25 (58%) had a ≥2-point decrease. All 10 subjects with advanced fibrosis or cirrhosis at baseline (Ishak Fibrosis Score of 4, 5 or 6) had a ≥1 point decrease (median decrease from baseline was 1.5 points). At the time of the long-term biopsy, all subjects had HBV DNA < 300 copies/mL and 49 (86%) had serum ALT ≤1 x ULN. All 57 subjects remained positive for HBsAg.

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

18. Patient counseling information

Information about treatment

Physicians should inform their patients of the following important points when initiating entecavir treatment:

- Patients should remain under the care of a physician while taking entecavir. They should discuss any new symptoms or concurrent medications with their physician.
- Patients should be advised that treatment with entecavir has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination.
- Patients receiving a 1-mg dose of entecavir should be advised to take it on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal). For nucleoside-naïve patients, the 0.5mg dose of entecavir can be taken with or without food.
- Patients should be advised to take a missed dose as soon as remembered unless it is almost time for the next dose. Patients should not take two doses at the same time.
- Patients should be advised that treatment with entecavir will not cure HBV.
- Patients should be informed that entecavir may lower the amount of HBV in the body, may lower the ability of HBV to multiply and infect new liver cells, and may improve the condition of the liver.
- Patients should be informed that it is not known whether entecavir will reduce their chances of getting liver cancer or cirrhosis.

Post-treatment exacerbation of Hepatitis

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.

HIV/HBV Co-infection

Patients should be offered HIV antibody testing before starting entecavir therapy. They should be informed that if they have HIV infection and are not receiving effective HIV treatment entecavir may increase the chance of HIV resistance to HIV medication.

19. Packaging

Blister of 10 tablets. Box of 3 blisters.

20. Storage condition, shelf-life

Do not store above 30°C.

The expiry date of this pack is printed on the box. Do not use this pack after this date.

21. Name, address of manufacturer

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