

**HIGHLIGHTS OF PRESCRIBING INFORMATION** These highlights do not include all the information needed to use ENTECAVIR TABLETS safely and effectively. See full prescribing information for ENTECAVIR TABLETS.

## ENTECAVIR tablets, for oral use

Initial U.S. Approval: 2005

**WARNING: SEVERE ACUTE EXACERBATIONS OF HEPATITIS B, PATIENTS CO-INFECTED WITH HIV AND HBV, AND LACTIC ACIDOSIS AND HEPATOMEGALY**  
*See full prescribing information for complete boxed warning.*

- 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 for at least several months after discontinuation. Initiation of anti-hepatitis B therapy may be warranted. (5.1)
- Entecavir tablets are not recommended for patients co-infected with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) who are not also receiving highly active antiretroviral therapy (HAART), because of the potential for the development of resistance to HIV nucleoside reverse transcriptase inhibitors. (5.2)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogue inhibitors. (5.3)

### INDICATIONS AND USAGE

Entecavir is a hepatitis B virus nucleoside analogue reverse transcriptase inhibitor indicated for the treatment of chronic hepatitis B virus infection in adults and children at least 2 years of age with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. (1)

### DOSAGE AND ADMINISTRATION

- Nucleoside-inhibitor-treatment-naïve with compensated liver disease (greater than or equal to 16 years old): 0.5 mg once daily. (2.2)

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**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* (5.1)].

Limited clinical experience suggests there is a potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if entecavir tablets are used to treat chronic hepatitis B virus (HBV) infection in patients with HIV infection that is not being treated. Therapy with entecavir tablets are not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART) (see *Warnings and Precautions* (5.2)).

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogue inhibitors alone or in combination with antiretrovirals [see *Warnings and Precautions* (5.3)].

#### 1 INDICATIONS AND USAGE

Entecavir tablets are indicated for the treatment of chronic hepatitis B virus infection in adults and pediatric patients 2 years of age and older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

#### 2 DOSAGE AND ADMINISTRATION

##### 2.1 Timing of Administration

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

##### 2.2 Recommended Dosage in Adults

##### Compensated Liver Disease

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

The recommended dose of entecavir tablets in adults and adolescents (at least 16 years of age) with a history of hepatitis B viremia while receiving lamivudine or known lamivudine or telbivudine resistance substitutions rM204I/V with or without rL180M, rL80I/V, or rV173L is 1 mg once daily.

##### Decompensated Liver Disease

The recommended dose of entecavir tablets for chronic hepatitis B virus infection in adults with decompensated liver disease is 1 mg once daily.

##### 2.3 Recommended Dosage in Pediatric Patients

Table 1 describes the recommended dose of entecavir for pediatric patients 2 years of age or older and weighing at least 10 kg. The oral solution should be used for patients with body weight up to 30 kg.

**Table 1: Dosing Schedule for Pediatric Patients**

Body Weight (kg)	Recommended Once-Daily Dose of Oral Solution (mL)	
	Treatment-Naïve Patients <sup>a</sup>	Lamivudine-Experienced Patients <sup>b</sup>
10 to 11	3	6
greater than 11 to 14	4	8
greater than 14 to 17	4	10
greater than 17 to 20	5	12
greater than 20 to 23	7	14
greater than 23 to 26	8	16
greater than 26 to 30	9	18
greater than 30	10	20

<sup>a</sup> Children with body weight greater than 30 kg should receive 10 mL (0.5 mg) of oral solution or one 0.5 mg tablet once daily.

<sup>b</sup> Children with body weight greater than 30 kg should receive 20 mL (1 mg) of oral solution or one 1 mg tablet once daily.

##### 2.4 Renal Impairment

In adult subjects with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased [see *Clinical Pharmacology* (12.3)]. 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 2. The once-daily dosing regimens are preferred.

Creatinine Clearance (mL/min)	Usual Dose (0.5 mg)		Lamivudine-Refractory or Decompensated Liver Disease (1 mg)	
	Usual Dose (0.5 mg)	Frequency	Usual Dose (1 mg)	Frequency
50 or greater	0.5 mg once daily	OR	1 mg once daily	OR
30 to less than 50	0.25 mg once daily <sup>a</sup>	OR	0.5 mg once daily	OR
	0.5 mg every 48 hours	OR	1 mg every 48 hours	OR
	0.5 mg once daily <sup>a</sup>	OR	0.3 mg once daily <sup>a</sup>	OR
10 to less than 30	0.15 mg every 72 hours	OR	0.2 mg every 72 hours	OR
Less than 10	0.05 mg once daily <sup>a</sup>	OR	0.1 mg once daily <sup>a</sup>	OR
Hemodialysis <sup>b</sup> or CAPD	0.5 mg every 7 days	OR	1 mg every 7 days	OR

<sup>a</sup> For doses less than 0.5 mg, entecavir oral solution is recommended.

<sup>b</sup> If administered on a hemodialysis day, administer entecavir tablets after the hemodialysis session.

• Nucleoside-inhibitor-treatment-naïve and lamivudine-experienced pediatric patients at least 2 years of age and weighing at least 10 kg; dosing is based on weight. (2.3)

• Lamivudine-refractory or known lamivudine or telbivudine resistance substitutions (greater than or equal to 16 years old): 1 mg once daily. (2.2)

• Decompensated liver disease (adults): 1 mg once daily. (2.2)

• Renal impairment: Dosage adjustment is recommended if creatinine clearance is less than 50 mL/min. (2.4)

• Entecavir tablets should be administered on an empty stomach. (2.1)

### DOSAGE FORMS AND STRENGTHS

• Tablets: 0.5 mg and 1 mg (3, 16)

### CONTRAINDICATIONS

• None. (4)

### WARNINGS AND PRECAUTIONS

- Severe acute exacerbations of hepatitis B virus infection after discontinuation: Monitor hepatic function closely for at least several months. (5.1, 6.1)
- Co-infection with HIV: Entecavir is not recommended unless the patient is also receiving HAART. (5.2)
- Lactic acidosis and severe hepatomegaly with steatosis: If suspected, treatment should be suspended. (5.3)

### ADVERSE REACTIONS

• In adults, the most common adverse reactions (≥3%, all severity grades) are headache, fatigue, dizziness, and nausea. The adverse reactions observed in pediatric patients were consistent with those observed in adults. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Carlsbad Technology, Inc. at 1-760-431-8284 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### USE IN SPECIFIC POPULATIONS

- Liver transplant recipients: Limited data on safety and efficacy are available. (8.8)

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Although there are insufficient data to recommend a specific dose adjustment of entecavir in pediatric patients with renal impairment, a reduction in the dose or an increase in the dosing interval similar to adjustments for adults should be considered.

#### 2.5 Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

#### 2.6 Duration of Therapy

The optimal duration of treatment with entecavir tablets 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 DOSAGE FORMS AND STRENGTHS

- Entecavir Tablets, 0.5 mg are white to off-white, triangular-shaped film-coated tablets, debossed with “YSP” on one side and “222” on the other side.
- Entecavir Tablets, 1 mg are pink, triangular-shaped film-coated tablets, debossed with “YSP” on one side and “216” on the other side.

#### 4 CONTRAINDICATIONS

None.

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 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* (6.1)]. 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.

##### 5.2 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* (12.4)]. 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.

##### 5.3 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 analogue inhibitors, including entecavir, alone or in combination with antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside inhibitor exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogue inhibitors 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).

#### 6 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* (5.1)].
- Lactic acidosis and severe hepatomegaly with steatosis [see *Boxed Warning, Warnings and Precautions* (5.3)].

#### 6.1 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.

##### Clinical Trial Experience in Adults

##### 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, 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 3.

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

<sup>a</sup> Includes events of possible, probable, certain, or unknown relationship to treatment regimen. Studies A1463022 and A1463027.

<sup>b</sup> 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 4.

**Table 4: Selected Treatment-Emergent Laboratory Abnormalities Reported in Four Entecavir Clinical Trials Through 2 Years**

Test	Nucleoside-Inhibitor-Naïve <sup>b</sup>		Lamivudine-Refractory <sup>c</sup>	
	Entecavir 0.5 mg n=668	Lamivudine 100 mg n=183	Entecavir 1 mg n=183	Lamivudine 100 mg n=190
<b>Any Grade 3-4 laboratory abnormality<sup>d</sup></b>	35%	36%	37%	45%
ALT > 10 × ULN and >2 × baseline	2%	4%	2%	11%
ALT > 5 × ULN	11%	16%	12%	24%
Albumin < 2.5 g/dL	< 1%	< 1%	0	2%
Total bilirubin > 2.5 × ULN	2%	2%	3%	2%
Lipase ≥ 2.1 × ULN	7%	6%	7%	7%
Creatinine > 3 × 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 <sup>e</sup>	4%	3%	4%	6%
Hematuria <sup>f</sup>	9%	10%	9%	6%
Platelets < 50,000/mm <sup>3</sup>	< 1%	< 1%	< 1%	< 1%

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

<sup>b</sup> Studies A1463022 and A1463027.

<sup>c</sup> 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.

<sup>d</sup> Includes hematology, routine chemistries, renal and liver function tests, pancreatic enzymes, and urinalysis.

<sup>e</sup> Grade 3 = 3+, large, ≥500 mg/dL; Grade 4 = 4+, marked, severe.

<sup>f</sup> Grade 3 = 3+, large; Grade 4 = 2+, 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<sub>10</sub>/mL reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

##### Exacerbations of Hepatitis After Discontinuation of Treatment

An exacerbation of hepatitis or ALT flare was defined as ALT greater than 10 times 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 5 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* (5.1)].

**Table 5: Exacerbations of Hepatitis During Off-Treatment Follow-up, Subjects in Studies A1463022, A1463027, and A1463026**

Subjects with ALT Elevations > 10 × ULN and > 2 × Reference <sup>a</sup>	Entecavir	Lamivudine
	Nucleoside-inhibitor-naïve	
HBeAg-positive	4/174 (2%)	13/147 (9%)
HBeAg-negative	24/302 (8%)	30/270 (11%)
Lamivudine-refractory	6/52 (12%)	0/16

<sup>a</sup> 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 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 [see *Clinical Studies* (14.1)]. 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 × baseline and > 10 × ULN) through Week 48. Eleven of 102 (11%) subjects treated with entecavir and 11/89 (13%) subjects treated with adefovir dip



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* (2.4)].

**Hepatic impairment.** The pharmacokinetics of entecavir following a single 1 mg dose were studied in adult 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 hepatic impairment and healthy control subjects; therefore, no dosage adjustment of entecavir is recommended for patients with hepatic impairment. The pharmacokinetics of entecavir have not been studied in pediatric subjects 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* (8.8)].

**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, 2D6, 3A4, 2B6, and 2E1. At concentrations up to approximately 340-fold higher than those observed in humans, entecavir did not induce the human CYP450 enzymes 1A2, 2C9, 2C19, 3A4, 3A5, and 2B6. 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* (7)].

## 12.4 Microbiology

### Mechanism of Action

Entecavir, a deoxyguanosine 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  $\alpha$ ,  $\beta$ , and  $\delta$  and mitochondrial DNA polymerase  $\gamma$  with  $K_i$  values ranging from 18 to  $> 160$   $\mu$ M.

### Antiviral Activity

Entecavir inhibited HBV DNA synthesis (50% reduction, EC<sub>50</sub>) at a concentration of 0.004  $\mu$ M in human HepG2 cells transfected with wild-type HBV. The median EC<sub>50</sub> value for entecavir against lamivudine-resistant HBV (rHL180M, rtM204V) was 0.026  $\mu$ M (range 0.010–0.059  $\mu$ M). 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 either NRTIs or zalcitabine at concentrations greater than 100 times the C<sub>max</sub> 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<sub>50</sub> values ranging from 0.026 to  $> 10$   $\mu$ M; the lower EC<sub>50</sub> 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 rL180M along with additional substitutions at residues rT184, rT502, or rM250, or a combination of these substitutions with or without an rI169 substitution in the HBV reverse transcriptase. Lamivudine-resistant strains harboring rL180M plus rM204V in combination with the amino acid substitution rtA181C conferred 16- to 122-fold reductions in entecavir phenotypic susceptibility.

#### Clinical Studies

**Nucleoside-inhibitor-naïve subjects:** Genotypic evaluations were performed on evaluable samples ( $> 300$  copies/mL serum HBV DNA) from 562 subjects who were treated with entecavir for up to 96 weeks in nucleoside-inhibitor-naïve studies (A1463022, A1463027, and rollover study A1463901). By Week 96, evidence of emerging amino acid substitution rs202G with rL180M and rM204V substitutions was detected in the HBV of 2 subjects (2/562<math>< 1\%\geq 1 log<sub>10</sub> increase above nadir). In addition, emerging amino acid substitutions at rM204I/V and rL180I, rV173I, or rL180M, which conferred decreased phenotypic susceptibility to entecavir in the absence of rT184, rT502, or rM250 changes, were detected in the HBV of 3 subjects (3/562<math>< 1\%< 300 copies/mL at end of dosing (up to 96 weeks).

HBeAg-positive (n=243) and -negative (n=39) treatment-naïve subjects who failed to achieve the study-defined complete response by 96 weeks were offered continued entecavir treatment in a rollover study. Complete response for HBeAg-positive was  $< 0.7$  MEQ/mL (approximately  $7 \times 10^6$  copies/mL serum HBV DNA) and HBeAg loss and, for HBeAg-negative was  $< 0.7$  MEQ/mL HBV DNA and ALT normalization. Subjects received 1 mg entecavir once daily for up to an additional 144 weeks. Of these 282 subjects, 141 HBeAg-positive and 8 HBeAg- negative subjects entered the long-term follow-up rollover study and were evaluated for entecavir resistance. Of the 149 subjects entering the rollover study, 88% (131/149), 92% (137/149), and 92% (137/149) attained serum HBV DNA  $< 300$  copies/mL by Weeks 144, 192, and 240 (including end of dosing), respectively. No novel entecavir resistance-associated substitutions were identified in a comparison of the genotypes of evaluable isolates with their respective baseline isolates. The cumulative probability of developing rT184, rT502, or rM250 entecavir resistance-associated substitutions (in the presence of rL180M and rM204V substitutions) at Weeks 48, 96, 144, 192, and 240 was 0.2%, 0.5%, 1.2%, 1.2%, and 1.2%, respectively.

**Lamivudine-refractory subjects:** Genotypic evaluations were performed on evaluable samples from 190 subjects treated with entecavir for up to 96 weeks in studies of lamivudine-refractory HBV (A1463026, A1463014, A1463015, and rollover study A1463901). By Week 96, resistance-associated amino acid substitutions at rT184, rT502, or rM250, with or without rI169 changes, in the presence of amino acid substitutions rM204I/V with or without rL80V, rV173L/M, or rL180M emerged in the HBV from 22 subjects (22/190=12%), 16 of whom experienced virologic rebound ( $\geq 1$  log<sub>10</sub> increase above nadir) and 4 of whom were never suppressed  $< 300$  copies/mL. The HBV from 4 of these subjects had entecavir resistance substitutions at baseline and acquired further changes on entecavir treatment. In addition to the 22 subjects, 3 subjects experienced virologic rebound with the emergence of rM204I/V and rL80V, rV173L/M, or rL180M. For isolates from subjects who experienced virologic rebound with the emergence of resistance-associated substitutions (n=19), the median fold-change in entecavir EC<sub>50</sub> values from reference was 19-fold at baseline and 106-fold at the time of virologic rebound. For subjects who continued treatment beyond 48 weeks, 40% (31/77) had HBV DNA  $< 300$  copies/mL at end of dosing (up to 96 weeks). Lamivudine-refractory subjects (n=157) who failed to achieve the study-defined complete response by Week 96 were offered continued entecavir treatment. Subjects received 1 mg entecavir once daily for up to an additional 144 weeks. Of these subjects, 80 subjects entered the long-term follow-up study and were evaluated for entecavir resistance. By Weeks 144, 192, and 240 (including end of dosing), 34% (27/80), 35% (28/80), and 36% (29/80), respectively, attained HBV DNA  $< 300$  copies/mL. The cumulative probability of developing rT184, rT502, or rM250 entecavir resistance-associated substitutions (in the presence of rM204I/V with or without rL180M substitutions) at Weeks 48, 96, 144, 192, and 240 was 6.2%, 15%, 36.3%, 46.6%, and 51.5%, respectively. The HBV of 6 subjects developed rA181G/S/T amino acid substitutions while receiving entecavir, and 4 developed entecavir resistance-associated substitutions at rT184, rT502, or rM250 and 1 had an rT184S substitution at baseline. Of 7 subjects whose HBV had an rI181R substitution at baseline, 2 also had substitutions at rT184, rT502, or rM250 at baseline and another 2 developed them while on treatment with entecavir.

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 rL180M plus rM204V.

#### Cross-resistance

Cross-resistance has been observed among HBV nucleoside analogue inhibitors. In cell-based assays, entecavir had 8- to 30-fold less inhibition of HBV DNA synthesis for HBV containing lamivudine and telbivudine resistance-associated substitutions rM204I/V with or without rL180M than for wild-type HBV. Substitutions rM204I/V with or without rL80I/V, rV173L, or rL180M, which are associated with lamivudine and telbivudine resistance, also confer decreased phenotypic susceptibility to entecavir. The efficacy of entecavir against

HBV harboring adenosine 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 rA181V or rN236T had 1.1- or 0.3-fold shifts in susceptibility to entecavir in cell culture, respectively.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

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 *Adverse Reactions* (6.2)].

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.

#### Mutagenesis

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.

#### Impairment of fertility

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.

## 14 CLINICAL STUDIES

### 14.1 Outcomes in Adults

#### At 48 Weeks

The safety and efficacy of entecavir in adults were evaluated in three Phase 3 active-controlled trials. 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.

#### Nucleoside-inhibitor-naïve Subjects with Compensated Liver Disease

**HBeAg-positive:** Study A1463022 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-inhibitor-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- $\alpha$ . At baseline, subjects had a mean Knodell Neuroinflammatory Score of 7.8, mean serum HBV DNA as measured by Roche COBAS AmpliCor<sup>®</sup> PCR assay was 9.66 log<sub>10</sub> copies/mL, and mean serum ALT 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 A1463027 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-inhibitor-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- $\alpha$ . At baseline, subjects had a mean Knodell Neuroinflammatory Score of 7.8, mean serum HBV DNA measured by Roche COBAS AmpliCor PCR assay was 7.58 log<sub>10</sub> copies/mL, and mean serum ALT level was 142 U/L. Paired, adequate liver biopsy samples were available for 88% of subjects. In Studies A1463022 and A1463027, entecavir was superior to lamivudine on the primary efficacy endpoint of Histologic Improvement, defined as a 2-point or greater reduction in Knodell Neuroinflammatory 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.

	Histologic Improvement and Change in Ishak Fibrosis Score at Week 48, Nucleoside-Inhibitor-Naïve Subjects in Studies A1463022 and A1463027			
	Study A1463022 (HBeAg-Positive)		Study A1463027 (HBeAg-Negative)	
	Entecavir 0.5 mg n=314 <sup>a</sup>	Lamivudine 100 mg n=314 <sup>a</sup>	Entecavir 0.5 mg n=296 <sup>a</sup>	Lamivudine 100 mg n=287 <sup>a</sup>
<b>Histologic Improvement (Knodell Scores)</b>				
Improvement <sup>b</sup>	72%	62%	70%	61%
No improvement	21%	24%	19%	26%
<b>Ishak Fibrosis Score</b>				
Improvement <sup>c</sup>	39%	35%	36%	38%
No change	46%	40%	41%	34%
Worsening <sup>c</sup>	8%	10%	12%	15%
Missing Week 48 biopsy	7%	14%	10%	13%
<sup>a</sup> Subjects with evaluable baseline histology (baseline Knodell Neuroinflammatory Score $\geq 2$ ).				
<sup>b</sup> $\geq 2$ -point decrease in Knodell Neuroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.				
<sup>c</sup> For Ishak Fibrosis Score, improvement = $\geq 1$ -point decrease from baseline and worsening = $\geq 1$ -point increase from baseline.				
<b>Table 10:</b>	Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Nucleoside-Inhibitor-Naïve Subjects in Studies A1463022 and A1463027			
	Study A1463022 (HBeAg-Positive)		Study A1463027 (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 <sup>a</sup>				
Proportion undetectable (< 300 copies/mL)	67%	36%	90%	72%
Mean change from baseline (log <sub>10</sub> copies/mL)	-6.86	-5.39	-5.04	-4.53
ALT normalization ( $\leq 1 \times$ ULN)	68%	60%	78%	71%
HBeAg seroconversion	21%	18%	NA	NA
<sup>a</sup> 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.				
<i>Lamivudine-refractory Subjects with Compensated Liver Disease</i>				
Study A1463026 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- $\alpha$ . The mean duration of prior lamivudine therapy was 2.7 years, and 85% had lamivudine resistance substitutions at baseline by an investigational line probe assay. At baseline, subjects had a mean Knodell Neuroinflammatory Score of 6.5, mean serum HBV DNA as measured by Roche COBAS AmpliCor PCR assay was 9.36 log <sub>10</sub> copies/mL, and mean serum ALT level was 128 U/L. Paired, adequate liver biopsy samples were available for 87% of 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.

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

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

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

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

	Selected Virologic, Biochemical, and Serologic Endpoints at Week 48, Lamivudine-Refractory Subjects in Study A1463026	
	Entecavir 1 mg n=141	Lamivudine 100 mg n=145
HBV DNA <sup>a</sup>		
Proportion undetectable (< 300 copies/mL)	19%	1%
Mean change from baseline (log <sub>10</sub> copies/mL)	-5.11	-0.48
ALT normalization ( $\leq 1 \times$ ULN)	61%	15%
HBeAg seroconversion	8%	3%
<sup>a</sup> Roche COBAS AmpliCor PCR assay (LLOQ = 300 copies/mL).		

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

#### Subjects with Decompensated Liver Disease

Study A1463048 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- $\alpha$ . In Study A1463048, 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<sub>10</sub> 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.

	Selected Endpoints at Week 48, Subjects with Decompensated Liver Disease, Study A1463048	
	Entecavir 1 mg n=100 <sup>a</sup>	Adefovir Dipivoxil 10 mg n=91 <sup>a</sup>
HBV DNA <sup>b</sup>		
Proportion undetectable (< 300 copies/mL)	57%	20%
Stable or improved CTP score <sup>c</sup>	61%	67%
HBeAg loss	5%	0
Normalization of ALT ( $\leq 1 \times$ ULN) <sup>d</sup>	49/78 (63%)	33/71 (46%)

<sup>a</sup> Endpoints were analyzed using intention-to-treat (ITT) method, treated subjects as randomized.

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

<sup>c</sup> Defined as decrease or no change from baseline in CTP score.

<sup>d</sup> Denominator is subjects with abnormal values at baseline.

ULN=upper limit of normal.

#### Subjects Co-infected with HIV and HBV

Study A1463038 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<sub>10</sub> 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<sub>10</sub> 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 [see *Warnings and Precautions* (5.2)].

	Virologic and Biochemical Endpoints at Week 24, Study A1463038	
	Entecavir 1 mg <sup>a</sup> n=51	Placebo <sup>a</sup> n=17
HBV DNA <sup>a</sup>		
Proportion undetectable (<300 copies/mL)	6%	0
Mean change from baseline (log <sub>10</sub> copies/mL)	-3.65	+0.11
ALT normalization ( $\leq 1 \times$ ULN)	34% <sup>c</sup>	8% <sup>c</sup>
<sup>a</sup> All subjects also received a lamivudine-containing HAART regimen.		
<sup>b</sup> Roche COBAS AmpliCor PCR assay (LLOQ = 300 copies/mL).		
<sup>c</sup> Percentage of subjects with abnormal ALT ( $> 1 \times$ 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<sub>10</sub> copies/mL, and 37% of subjects with abnormal ALT at baseline had ALT normalization ( $\leq 1 \times$  ULN).

#### 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  $< 1.25 \times$  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  $< 1.25 \times$  ULN (HBeAg-negative) continued blinded dosing through 96 weeks or until the response criteria were met