## INDICATIONS AND USAGE

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

The following points should be considered when initiating therapy with Entecavi

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

Virologic, biochemical, serologic, and safety data are available for a limited number of adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy [see Warnings and Precautions

## DOSAGE AND ADMINISTRATION

and Clinical Studies].

## 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 ( $\geq$  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) Renal Impairment

In subjects with renal impairment, the apparent oral clearance of entecayir decreased as creatinine clearance decreased [see Clinical Pharmacology]. 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.

Creatinine Clearance (mL/min)	Usual Dose (0.5 mg)	Lamivudine-Refractory or Decompensated Liver Disease (1
≥50	0.5 mg once daily	1 mg once daily
30 to < 50	0.5 mg every 48 hours	0.5 mg once daily <b>OR</b> 1 mg every 48 hours
10 to < 30	0.5 mg every 72 hours	1 mg every 72 hours
< 10 Hemodialysis <sup>b</sup> or CAPD	0.5 mg every 7 days	1 mg every 7 days

No dosage adjustment is necessary for patients with hepatic impairment.

**Duration of Therapy** The optimal duration of treatment with ENTECAVIR for patients with chronic hepatitis B virus infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular

## CONTRAINDICATIONS

ENTECAVIR is contraindicated in patients with previously demonstrated hypersensitivity to entecavir or any component of the product. WARNINGS AND PRECAUTIONS

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]. 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.

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*]. 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. 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

y (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations) 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

benjane with rates in parents with compensate unclaim. Asso, parents with accompensate a real reason and the art rights have to fact the parents and specific Precaution (see Adverse Reactions). Resistance and Specific Precaution for Lamivudine-Refractory Patients Mutations in the HBV polymerase that encode lamivudine-resistance substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with entecavir associated ance (ETVr). In a small percentage of lamivudine-refractory patients, ETVr substitutions at residues rt T184, rt \$202 or rt M250 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

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-resistantHBV, combination use of entecavir plus a second antiviral agent (which does not share cross-resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy [see Clinical Pharmacology 1.

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].

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

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 lamivuding (n = 858) for up to 2 years. Median duration of therapy was 69 weeks for ENTECAVIRtreated 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 Al463026 and Al463014. The safety profiles of ENTECAVIR and lamivudine were comparable in these studies. The most common adverse reactions of any severity (  $\geq$  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

Nucleoside-Naïve			Lamivudir	ne-Refractory <sup>c</sup>
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 <sup>a</sup>	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%

<sup>b</sup>Studies Al463022 and Al463027. fincludes 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.

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' Laboratory Abnormalities Reported in Four Entecavir Clinical Trials Through 2 Years

	Nucle	oside-Naïve <sup>b</sup>	Lamivudi	ne-Refractory <sup>c</sup>
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 <sup>d</sup>	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 <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%

\* 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. <sup>b</sup> Studies Al463022 and Al463027.

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  $1\,mg)\,once\,daily\,versus\,continued\,lamivudine\,100\,mg\,once\,daily\,for\,up\,to\,52\,weeks\,in\,subjects\,who\,experienced\,recurrent\,viremia\,on\,lamivudine\,therapy.$ les hematology, routine chemistries, renal and liver function tests, pancreatic enzymes, and urinalysis.

 $^{\circ}$ Grade 3 = 3+, large,  $\geq$  500 mg/dL; Grade 4 = 4+, marked, severe. '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  $\geq 2\log_{10}/mL$  reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment. Exacerbations of Hepatitis after Discontinuation of Treatment An exacerbation of hepatitis or ALT flare was defined as ALT greater than 10 times the upper limit of normal (ULN) and greater than 2 times the subject's reference level (minimum of the baseline or last

measurement at end of dosing). For all subjects who discontinued treatment (regardless of reason), Table 4 presents the proportion of subjects in each study who experienced post-treatment ALT flares. In these studies, a subset of subjects was allowed to discontinue treatment at or after 52 weeks if they achieved a protocol-defined response to therapy. If ENTECAVIR is discontinued without regard to treatment response, the rate of post-treatment flares could be higher (see also Warnings and Precautions 

Subjects with ALT Elevations > 10 X ULN and > 2 X Reference\* Entecavir Lamivudine Nucleoside-naïve 13/147 (9%) HBeAg-positive 4/174 (2%) HBeAg-negative 6/52 (12%) 0/16

# \*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 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 [see Clinical Studies]. Among the 102 subjects receiving Entecavir, the most common treatment-emi ring through Week 48 were peripheral edema (16%), ascites (15%), pyre any severity, regardless of causality, occi

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%). Fighteen of 102 (18%) subjects treated with Entecavir and 18/89 (20%) subjects treated with adefovir digivoxil died during the first 48 weeks of therapy. The majority of deaths (11 in the Entecavir ground 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  $(13\%) \, subjects \, treated \, with \, a defovir \, dipivoxil \, had \, a \, confirmed \, increase \, in \, serum \, creatinine \, of \, 0.5 \, mg/dL \, through \, Week \, 48.$ 

The safety profile of Entecavir 1 mg (n = 51) in HIV/HBV co-infected subjects enrolled in Study Al463038 was similar to that of placebo (n = 17) through 24 weeks of blinded treatment and similar to that seen in non-HIV infected subjects [see Warnings and Precautions].

Liver Transplant Recipients Among 65 subjects receiving Entecavir in an open-label, post-liver transplant trial [see Use in Specific Populations], 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 Al463080 was a randomized, global, observational, open-label Phase 4 study to assess long-term risks and benefits of ENTECAVIR(0.5 mg/day) treatment as compared to other standardof-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. Or many, increased and 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)lides, 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 below Table.

Table 5: Principal Analyses of Time to Adjudicated Events - Randomized Treated Subjects Number of subjects with events

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ENTECAVIR N=6216	Non-ETV N=6162	Hazard Ratio (ENTECAVIR: Non- ETV) (CI <sup>a</sup> )
331	337	0.93 (0.800, 1.084)
350	375	0.89 (0.769, 1.030)
238	264	0.85 (0.713, 1.012)
95	81	1.10 (0.817, 1.478)
240 <sup>b</sup>	263	0.87 (0.727, 1.032)
	331 350 238	N=6216 N=6162  331 337 350 375 238 264  95 81

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. 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

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 vered 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 exp

Immune system disorders: Anaphylactic reaction Metabolism and nutrition disorders: Lactic acidosis Hepatobiliary disorders: Increased transamina

Skin and subcutaneous tissue disorders: Alopecia, rash.

Since entecavir is primarily eliminated by the kidneys [see Clinical Pharmacology], 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.

USE IN SPECIFIC POPULATIONS Pregnancy

acquisition of HBV.

Geriatric Use

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

Developmental toxicity studies were performed in rats and rabbits. There were no signs of embryofetal or maternal toxicity when pregnant animals received oral entecavir at approximately 28 (rat) and 212 (rabbit) times the human exposure achieved at the highest recommended human dose of 1 mg/day. In rats, maternal toxicity, embryofetal toxicity (resorptions), lower fetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternebrae, and phalanges), and extra lumbar 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** 

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

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

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

Clinical studies of Entecavir did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Entecavir is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Dosage and Administration]. 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 HBeAgpositive, the mean baseline HBV DNA was 7.0 log, 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 Because of low enrollment, safety and efficacy have not been established in the US Hispanic population.

Dosage adjustment of Entecavir is recommended for patients with creatinine clearance less than 50 mL/min, including patients on hemodialysis or CAPD [see Dosage and Administration and Clinical

Pharmacology]. Liver Transplant Recipients

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, 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

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. Eliqible subjects who had HBV

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 virenia. 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.

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 t

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 [see Dosage and Administration and Clinical Pharmacology].

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

The chemical name for entecavir is, 2-amino-1, 9-dihydro-9-{(1S, 3R, 4S)-4hydroxy, 3-{hydroxymethyl}-2-methylenecyclopentyl]-6H-purin-6-one, monohydrate. Its molecular formula is C<sub>12</sub>H<sub>m</sub>N<sub>6</sub>O<sub>3</sub> H<sub>2</sub>O, and its molecular weight is 295.3. Entecavir is a white to off-white powder. It is slightly soluble in water (2.4 mg/mL), and the pH of the saturated solution in water is 7.9 at  $25^{\circ} \pm 0.5^{\circ}$  C. Entecavir has the following structural formula:

# CLINICAL PHARMACOLOGY

Entecavir is an antiviral drug [see Microbiology].

The single- and multiple-dose pharmacokinetics of entecavir were evaluated in healthy subjects and subjects with chronic henatitis B virus infection.

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,, 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, Cmax at steady state was 4.2 ng/mL and trough plasma concentration (Cmoonly) was 0.3 ng/mL. For a 1 mg oral dose, Cmax at steady state was 4.2 ng/mL and Cmoonly plasma concentration (Cmoonly) was 0.3 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  $C_{\rm max}$  of 44%-46%, and a decrease in AUC of 18%-20% [see *Dosage and Ad* 

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

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

Metabolism and Elimination Following administration of \*\*C-entecavir in humans and rats, no oxidative or acetylated metabolites were observed. Minor amounts of phase II metabolites (glucuronide and sulfate conjugates) were observed. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system [see Drug Interactions, below].

After reaching peak concentration, entecavir plasma concentrations decreased in a bi-exponential manner with a terminal elimination half-life of approximately 128-149 hours. The observed drug accumulation index is approximately 2-fold with once-daily dosing, suggesting an effective accumulation half-life of approximately 24 hours. Entecavir is predominantly eliminated by the kidney with urinary recovery of unchanged drug at steady state ranging from 62% to 73% of the administered dose. Renal clearance is independent of dose and ranges from 360 to 471 mL/min suggesting that entecavir undergoes both glomerular filtration and net tubular secretion [see Drug Interactions]

Special Populations 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

should be based on the renal function of the patient, rather than age [see Dosage and Administration]. 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 6 [see Dosage and Adm Table 6: Pharmacokinetic Parameters in Subjects with Selected Degrees of Renal Function

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

abic o. r narmacokinetio r arametero in	oubjects with ociected E	regrees of fields i unotio				
		Renal	Function Group			
		Baseline Creati	nine Clearance (mL/min)			
	Unimpaired > 80	Mild > 50· ≤ 80	Moderate 30-50	Severe < 30	Severe Managed with Hemodialysis	Severe Managed with CAPD
	n = 6	n = 6	n=6	n-6	n=6	n=4
Cmax (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) (ngh/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)

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 [see Dosage and Administration] 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 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

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 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 [se

Drug Interactions]. Microbiology

Mechanism of Action

Entecavir, a guanosine nucleoside analogue with activity against HBV reverse transcriptase (rt), is efficiently phosphorylated to the active triphosphate form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine triphosphate, entecavir triphosphate functionally inhibits all three activities of the HBV reverse transcriptase: (1) base priming, (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand of HBV DNA. Entecavir triphosphate is a weak inhibitor of cellular DNA polymerases α, β, and  $\delta$  and mitochondrial DNA polymerase  $\gamma$  with K values ranging from 18 to > 160  $\mu M$  . Entecavir inhibited HBV DNA synthesis (50% reduction, EC a) at a concentration of 0.004  $\mu$ M in human HepG2 cells transfected with wild-type HBV. The median EC value for entecavir against lamivu

resistant HBV (rtL180M, 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, lamivoline, stavudine, tendroir, 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<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 walues ranging from 0.026 to > 10  $\mu$ M; the lower EC 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 transcrip trations, confirming inhibitory pressure at high entecavir concentrations. HIV variants containing the M184V substitution showed loss of susceptibility to entecavir. at micromolar con

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 rtM204l/V with or without rtl. 180M along with additional substitutions at residues rt 1184, rt 15202, or rt M250, or a combination of these substitutions with or without an rtl 169 substitution in the HBV reverse transcriptase. Lamivudine-resistant strains harboring rt L180M plus rt M204V in combination with the amino acid substitution rt A181C conferred

In Clinical Studies Subjects in clinical trials initially treated with entecavir 0.5 mg (nucleoside-naïve, studies Al463022, Al463027, and rollover study Al463901) or 1.0 mg (lamivudine-refractory, studies Al463026, Al463014, Al463015, and rollover study Al463901) 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 7). These substitutions were observed only in the presence of lamivudine resistance- associated (LVDr) substitutions (rtM204V and rtL180M).

Table 7: Emerging Genotypic Entecavir Resistance I nrough Tear 3, Nucleoside-Naive Studies					
	Year 1	Year 2	Year 3°	Year 4°	Year 5°
Subjects treated and monitored for resistance <sup>b</sup>	663	278	149	121	108
Subjects in specific year with:					
- emerging genotypic ETVr <sup>c,d</sup>	1	1	1	0	0
- genotypic ETVr <sup>cd</sup> with virologic breakthrough <sup>e</sup>	1	0	1	0	0
Cumulative probability of:					
· emerging genotypic ETVr <sup>c,d</sup>	0.2%	0.5%	1.2%	1.2%	1.2%
· genotypic ETVr <sup>c,d</sup> with virologic breakthrough	0.2%	0.2%	0.8%	0.8%	0.8%
			•		

\*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) 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.

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). ETVr = entecavir resistance substitutions at residues rtT184, rtS202, or rtM250.

<sup>d</sup>Patients also had lamivudine resistance substitutions (rtM204V and rtL180M). ° ≥ 1 log., increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point.

16- to 122-fold reductions in entecavir phenotypic susceptibility.

Lamivudine-refractory subjects: ETVr substitutions (in addition to LVDr substitutions rtM204VII + rtl.180M) 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 ( $\geq$  1 log<sub>10</sub> increase above nadir). Emerging entecavir resistance in lamivudine-refractory studies through Week 240 is summarized in Table 8. Table 8: Emerging Genotypic Entecavir Resistance Through Year 5, Lamivudine-Refractory Studies

146	80	52	33
		6	2
		6	2
1.0			
14'	13'	9 <sup>t</sup>	1f
15%	36.3%	46.6%	54.45%
10.7%	27% <sup>f</sup>	41.3%	43.6%f
-			100,0

subjects in Year 4, and for 16 weeks for 1 of 33 subjects in Year 5 in a rollover study. cludes 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).

"ETVr = entecavir resistance substitutions at residues rtT184, rtS202, or rtM250. <sup>d</sup>Patients also had lamivudine resistance substitutions (rtM204V/I ± rtL180M).

1 log increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point. 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  $< 10^4 \, log_{10}$  contains the contains 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  $< 10^4 \, log_{10}$  contains 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). copies/mL by PCR at Week 24 had a lower rate of resistance than thosewho 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 rtl. 180M plus rtM204V

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

resistance substitutions (IM204) with or without it footh man for wheely per not substitutions (IM204) with or without it 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 falling 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.

## 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  $ded\ dose\ of\ 1\,mg/day.\ In\ mouse\ and\ rat\ studies,\ entecavir\ was\ positive\ for\ carcinogenic\ findings.$ 

In mice, lung adenomas were increased in males and females at exposures 3 and 40 times those in humans. Lung carcinomas in both male and female mice were increased at exposures 40 times those in humans. Combined lung adenomas and carcinomas were increased in male mice at exposures 3 times and in female mice at exposures 40 times those in humans. Tumor development was preceded by pneumocyte proliferation in the lung, which was not observed in rats, dogs, or monkeys administered entecavir, supporting the conclusion that lung tumors in mice may be a species-specific event.

Hepatocellular carcinomas were increased in males and combined liver adenomas and carcinomas were also increased at exposures 42 times those in humans. Vascular tumors in female mice (hemangiomas of ovaries and uterus and hemangiosarcomas of spleen) were increased at exposures 40 times those in humans. In rats, hepatocellular adenomas were increased in females at exposures 24 times those in or ovaries and orients and orientally said trends of specially were increased at exposures 40 times those in humans. In rais, negatocential adentification were increased in females at exposures 40 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. Skin fibromas were induced in females at exposures 4 times those in humans.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans. Entecavir was clastogenic to human lymphocyte cultures. Entecavir was not mutagenic in the Ames bacterial reverse mutation assay using S. typhimurium and E. coli strains in the presence or absence of metabolic activation, a mammalian-cell gene mutation assay, and a transformation assay with

Syrian hamster embryo cells. Entecavir was also negative in an oral micronucleus study and an oral DNA repair study in rats. In reproductive toxicology studies, in which animals were administered entecavir at up to 30 mg/kg for up to 4 weeks, no evidence of impaired fertility was seen in male or female rats at systemic exposures 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 CLINICAL STUDIES

The safety and efficacy of ENTECAVIR were evaluated in three Phase 3 active-controlled trials [see Clinical Studies [12.1] (12.2)]. These studies included 1633 subjects 16 years of ane 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 Clinical Studies]. Outcomes at 48 Weeks HBeAg-positive: Study Al463022 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-a. At baseline, subjects had a mean Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA as measured by Roche COBAS Amplicor PCR assay was 9.66 log<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-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-c. 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<sub>10</sub> copies/mL, and mean serum ALT level was 142 U/L. Paired, adequate liver biopsy samples were available for

In Studies Al463022 and Al463027, 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 Al463022 and Ai463027

	Study Al463022 (H	HBeAg-Positive)	Study AI463027 (HBeAg-Negative)	
	Entecavir 0.5 mg n=314*	Lamivudine 100 mg n=314°	Entecavir 0.5 mg n=296°	Lamivudine 100 mg n = 287°
Histologic Improvement (Knodell Scores)				
Improvement <sup>b</sup>	72%	62%	70%	61%
No improvement	21%	24%	19%	26%
Ishak Fibrosis Score 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%

 $^{\text{b}} \geq$  2-point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.

able 10: Selected Virologic, Biochemical, and Serolog	ic Endpoints at Week 48, Nucleosid	le-Naïve Subjects in Studies AI463	022 and AI463027	
	Study Al463022	(HBeAg-Positive)	Study Al463027 (HBeAg-Negative)	
	ENTECAVIR 0.5 mg	Lamivudine 100 mg n=355	ENTECAVIR 0.5 mg n=325	Lamivudine 100 mg n = 313
HBV DNA'				•
Proportion undetectable ( < 300 copies/mL)	67%	36%	90%	72%
Mean change from baseline log10 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 NA

a Roche COBAS Amplicor PCR assay flower limit of quantification (LLQQ) = 300 copies/mL1.

### Histologic Improvement was independent of baseline levels of HBV DNA or ALT. Lamivudine-refractory Subjects with Compensated Liver Disease

Study Al463026 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

COBAS Amplicor PCR assay was 9.36 log, 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 Al463026 Lamivudine 100 mg n=116 ° ENTECAVIR 1 mg n=124° Histologic Improvement (Knodell Scores) 55% 28% No improvement 34% 57% Ishak Fibrosis Score 34% 16% Improvement No change 44% 42% Worsening 11% 26%

 $^{\circ}$  Subjects with evaluable baseline histology (baseline Knodell Necroinflammatory Score  $\geq$  2). >2-point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis score 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, Lamiyudine-Refractory Subjects in Study Al463026

	ENTECAVIR 1 mg n = 141	Lamivudine 100 mg n = 145
HBV DNA <sup>3</sup>		
Proportion undetectable ( < 300 copies/mL)	19%	1%
Mean change from baseline (log10 copies/mL)	-5.11	-0.48
ALT normalization (≤ 1 X ULN)	61%	15%
HBeAg seroconversion	8%	3%
*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

Subjects Co-infected with HIV and HBV

Missing Week 48 biopsy

Study Al463048 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 HBeAq- 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 pre predominantly with lamivudine or interferon- $\alpha$ .

In Study Al463048, 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, 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.

	ENTECAVIR 1 mg n=100°	Adefovir Dipivoxil 10 mg n=91
HBV DNA <sup>5</sup>	·	·
Proportion undetectable ( < 300 copies/mL)	57%	20%
Stable or improved CTP score <sup>c</sup>	61%	67%
HBsAg loss	5%	0
Normalization of ALT (≤1 X ULN) <sup>d</sup>	49/78 (63%)	33/71 (46%)
a Endpoints were analyzed using intention-to-treat (ITT) method, treated subj	ects 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.		

Study Al463038 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 virenia 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., 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, 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 coinfection who have not received prior lamivudine therapy. Entecavir has not been evaluated in HIV/HBV co-infected patients who were not simultaneously

	ENTECAVIR 1 mg <sup>3</sup> n=51	Placebo³ n=17
IBV DNA <sup>b</sup>		
Proportion undetectable ( < 300 copies/mL)	6%	0
Mean change from baseline (log10 copies/mL)	-3.65	+0.11
ALT normalization (≤1 X ULN)	34%°	8%°
All subjects also received a lamivudine-containing HAART regimen.		
Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).		

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 "copies/mL, and 37% of subjects with abnormal ALT at baseline had ALT normalization (  $\leq 1$  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 achieved 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 A1463022), 243 (69%) Entecavir -treated subjects and 164 (46%) lamivudine-treated subjects contains a subject of the su 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 conjectmL by PCR at the end of dosing (up to 96 weeks). 193 (79%) Entecavir subjects achieved ALT  $\leq$  1 X ULN compared to 112 (68%) lamivudine subjects, and HBeAg seroconversion occurred in 26 (11%) Entecavir subjects and 20 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  $\leq$  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  $\leq$  1 X ULN, and 47 (70%) subjects sustained HBeAg seroconversion at the end of follow-up. de-naïve. HBeAg-negative subjects (Study Al463027). 26 (8%) Entecavir-treated subjects and 28 (9%) la

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  $\leq$  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 A1463022 (HBeAg- positive) and A1463027 (HBeAg-negative) who enrolled in a long-term rollover study were evaluated for longterm 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 laminudine (median duration 29 weeks). Of these subjects 56 (96%) had instological improvement as previously defined (see Table 10, footnote b), and 50 (88%) had a  $\geq$  1-point decrease in Ishak fibrosis score. For the 43 subjects with baseline Ishak Fibrosis Score  $\geq$  2, 25 (58%) had a  $\geq$  2-point decrease. All 10 subjects with advanced fibrosis or cirrhosis at baseline (Ishak Fibrosis Score of 4, 5 or 6) had a  $\geq$  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  $\leq$  1 x ULN. All 57 subjects remained positive for HBsAg. Laminudine-refractory subjects: Among laminudine-refractory subjects (Study Al463026), 77 (55%) Entecavir-treated subjects and 3 (2%) laminudine subjects continued blinded treatment for un to 96

weeks. In this cohort of Entecavir subjects, 31 (40%) subjects achieved HBV DNA < 300 copies/mL, 62 (81%) subjects had ALT  $\leq$  1 X ULN, and 8 (10%) subjects demonstrated HBeAg seroconversion at the end of dosing.

# HOW SUPPLIED/STORAGE AND HANDLING

Calcium Carbonate, Starch, Pregelatinized, Carmellose Sodium, Soy polysaccharides, Citric Acid Monohydrate and Sodium Stearyl FumarateEntecavir Tablets 0.5mg White to off white, triangle shaped, biconvex, film-coated tablets, debossed with 'J' on one side and '11 0' on the other side.

Pack Style

Entecavir Tablets 1mg Pink, triangle shaped, biconvex, film-coated tablets, debossed with 'J' on one side and '111' on the other side 8's Alu-Alu Blister Pack

# Storage Store below 30°C and protect from moisture.

PATIENT COUNSELLING INFORMATION Severe Acute Exacerbation of Hepatitis after Discontinuation of Treatment
Inform patients that discontinuation of anti-hepatitis B therapy, including Entecavir, may result in severe acute exacerbations of hepatitis B. Advise the patient to not discontinue Entecavir without first

Risk of Development of HIV-1 Resistance in Patients with HIV-1 Coinfection Inform patients that if they have or develop HIV infection and are not receiving effective HIV treatment, Entecavir may increase the risk of development of resistance to HIV medication Lactic Acidosis and Severe Hepatomegaly Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to . Advise patients to contact their healthcare provider immediately and stop

## Entecavir if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (See section Warnings and Precaution Keen TECAVIR and all medicines out of the reach of children General information about the safe and effective use of TECAVIR

informing their healthcare provider (See section Warnings and Precautions).

Patients should be advised that treatment with TECAVIR 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 0.5 mg dose of Entecavir can be taken with or without food. 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.

TECAVIR does not stop you from spreading the hepatitis B virus (HBV) to others by sex, sharing needles, or being exposed to your blood. Talk with your healthcare provider about safe sexual practices that protect your partner. Never share needles. Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.

Missed Dosage Inform patients that it is important to take Entecavir on a regular dosing schedule and to avoid missing doses as it can result in development of resistance (See section Dosage and Administration).

Treatment Duration Advise patients that in the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. The relationship between response and long-term prevention of outcomes such as hepatocellular carcinoma is not known.

### TECAVIR (Entecavir Tablets) What is the most important information I should know about TECAVIR?

Your hepatitis B virus (HBV) infection may get worse if you stop taking TECAVIR. This usually happens within 6 months after stopping TECAVIR.

Take TECAVIR exactly as prescribed.

Do not run out of TECAVIR.

Do not stop TECAVIR without talking to your healthcare provider. Your healthcare provider should monitor your health and do regular blood tests to check your liver if you stop taking TECAVIR.

If you have or get HIV that is not being treated with medicines while taking TECAVIR, the HIV virus may develop resistance to certain HIV medicines and become harder to treat. You should get an HIV test before you start taking TECAVIR and any time after that when there is a chance you were exposed to HIV. TECAVIR can cause serious side effects including:

3. Lactic acidosis (buildup of acid in the blood). Some people who have taken TECAVIR or medicines like TECAVIR (a nucleoside analogue) have developed a serious condition called lactic acidosis. Lactic acidosis is a serious medical emergency that can cause death. Lactic acidosis must be treated in the hospital. Reports of lactic acidosis with TECAVIR generally involved patients who were seriously ill due to their liver disease or other medical condition. Call your healthcare provider right away if you get any of the following signs or symptoms of lactic acidosis:

You feel very weak or tired.

You have unusual (not normal) muscle pain

You have trouble breathing You have stomach pain with nausea and vomiting.

You have a fast or irregular heartbeat.

4. Serious liver problems. Some people who have taken medicines like TECAVIR have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and Hepatomegaly with steatosis is a serious medical emergency that can cause death  ${\bf Call\ your\ health care\ provider\ right\ away\ if\ you\ get\ any\ of\ the\ following}$ 

signs or symptoms of liver problems: Your skin or the white part of your eyes turns yellow (jaundice).

Your urine turns dark.

Your bowel movements (stools) turn light in color. You don't feel like eating food for several days or longer

You feel sick to your stomach (nausea).

You have lower stomach pain

You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight, or have been taking nucleoside analogue medicines, like TECAVIR, for a long time. What is TECAVIR? TECAVIR is a prescription medicine used to treat chronic hepatitis B virus (HBV) in adults and children 2 years of age and older who have active liver disease

 TECAVIR will not cure HBV. TECAVIR may lower the amount of HBV in the body.

 TECAVIR may lower the ability of HBV to multiply and infect new liver cells. TECAVIR may improve the condition of your liver.

• It is not known whether TECAVIR will reduce your chances of getting liver cancer or liver damage (cirrhosis), which may be caused by chronic HBV infection It is not known if TECAVIR is safe and effective for use in children less than 2 years of age.

 $What should \ I \ tell \ my \ health care \ provider \ before \ taking \ TECAVIR?$ 

Before you take TECAVIR, tell your healthcare provider if you: have kidney problems. Your TECAVIR dose or schedule may need to be changed. have received medicine for HBV before. Some people, especially those who have already been treated with certain other medicines for HBV infection, may develop resistance to TECAVIR. These

people may have less benefit from treatment with TECAVIR and may have worsening of hepatitis after resistant virus appears. Your healthcare provider will test the level of the hepatitis B virus in your blood regularly. have any other medical conditions.

 are pregnant or plan to become pregnant. It is not known if TECAVIR will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant. are breastfeeding or plan to breastfeed. It is not known if TECAVIR can pass into your breast milk. You and your healthcare provider should decide if you will take TECAVIR or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you have taken a medicine to treat HBV in the past.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine. How should I take TECAVIR?

Take TECAVIR exactly as your healthcare provider tells you to.

 Your healthcare provider will tell you how much TECAVIR to take. Your healthcare provider will tell you when and how often to take TECAVIR.

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 0.5 mg dose of Entecavir can be taken with or without food. (See section Dosage and Administration). Do not change your dose or stop taking TECAVIR without talking to your healthcare provider. If you miss a dose of TECAVIR, take it as soon as you remember and then take your next dose at its regular time. If it is almost time for your next dose, skip the missed dose. Do not take two doses at the

same time. Call your healthcare provider or pharmacist if you are not sure what to do. When your supply of TECAVIR starts to run low, call your healthcare provider or pharmacy for a refill. **Do not run out of TECAVIR**. If you take too much TECAVIR, call your healthcare provider or go to the nearest emergency room right aw

What are the possible side effects of TECAVIR? TECAVIR may cause serious side effects. See "What is the most important information I should know about TECAVIR?"

The most common side effects of TECAVIR include:

tiredness

 dizziness nausea

Tell your healthcare provider if you have any side effect that bothers you or that does not go away

These are not all the possible side effects of TECAVIR. For more information, ask your healthcare provider or pharmacist How should I store TECAVIR?

 Store TECAVIR Tablets below 30 °C and protect from moisture Keep TECAVIR Tablets in a tightly closed container

 Store TECAVIR Tablets in the original carton, and keep the carton out of the light. Safely throw away TECAVIR that is out of date or no longer needed. Dispose of unused medicines through community take-back disposal programs when available or place TECAVIR in an

Product Owner address: **HETERO LABS LIMITED** 7-2-A 2, Hetero Corporate, Industrial Estates, Sanathnagar Hyderabad - 500 018, India. HETERO LABS LIMITED UNIT-V, TSIIC Formulation SEZ,

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