Prescribing Information for Entikav™ Dispersible Tablets

Please read the instruction carefully and use it under the direction of the physicians.

WARNINGS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported on using of nucleoside analogues alone or in combination with other antiretroviral drugs.

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 1. Exacerbations of Hepatitis after discontinuation of therapy).

Limited clinical experience suggests that there is a potential for the development of resistance to human immunodeficiency virus (HIV) nucleoside reverse transcriptase inhibitors if entecavir is used to treat chronic hepatitis B virus (HBV) infection in patients with HIV infection that is not being treated. Therapy with entecavir is not recommended for HIV/HBV co-infected patients who are not receiving highly active antiretroviral therapy (HAART). (See WARNINGS 3. Co-infection with HIV).

NAME OF MEDICINAL PRODUCT

Entikav™ Dispersible Tablets

COMPOSITION

Each dispersible tablet contains entecavir 0.5mg

EXCIPIENTS

Betacyclodextrin (dried basis), Microcrystalline Cellulose 101, Hyprolose, Polyplasdone XL, 70% Ethanol and Magnesium Stearate.

PHARMACEUTICAL FORM

White or almost white tablets.

INDICATIONS

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

DOSAGE AND ADMINISTRATION

The patient should take the product under the direction of the experienced physicians.

Recommended Dosage:

The recommended dose of this product for the adults and adolescents of 16 years old or older is 0.5mg once daily (1 tablet). The recommended dose of it is 1 mg once daily (two tablets) in the patients with a history of hepatitis B viremia while receiving lamivudine or with known lamivudine resistance mutations.

This product should be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal). This product may be swallowed or taken orally after dispersed with water.

Renal Impairment

In patients with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance declined (see Pharmacokinetics, special population). Dosage adjustment is recommended for the patients with creatinine clearance <50mL/min [including patients of hemodialysis or continuous ambulatory peritoneal dialysis (CAPD)], as shown in Table 1.

Table 1 The Recommended Dosage Interval Adjustment of Entecavir in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Usual Dose (0.5mg)	Lamivudine-Refractory (1mg)
≥50	0.5mg once daily	1mg once daily
30 to <50	0.5mg every 48 hours	1mg every 48 hours
10 to <30	0.5mg every 72 hours	1mg every 72 hours
<10 Hemodialysis * or CAPD	0.5mg every 5~7 days	1mg every 5~7 days

* The patients who receive hemodialysis should administer the drug after hemodialysis.

Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

Duration of Therapy

The optimal duration of treatment with this product and the relationship between treatment and long-term outcomes such as cirrhosis and hepatic carcinoma are unknown till now.

ADVERSE REACTIONS

Assessment of adverse reactions is based on 4 global clinical trials: AI463014, AI463022, AI463026 and AI463027 and 3 clinical trials conducted in China (AI463012, AI463023 and AI463056). 2,596 human subjects with chronic hepatitis B in total were enrolled in these 7 studies. In the control study with lamivudine, the adverse reactions and abnormal laboratory test results of entecavir were similar to those of lamivudine.

In the overseas studies, the most common adverse events of this product include: headache, fatigue, dizziness and nausea. The most common adverse events among lamivudine-treated patients were: headache, fatigue and dizziness. In these 4 studies, 1% of the entecavir-treated patients and 4% of the lamivudine-treated patients discontinued the study owing to adverse events or abnormal laboratory test results.

Overseas Clinical Adverse Events

Selected clinical adverse events of moderate-severe intensity and considered at least possibly related to the treatment occurring during therapy in 4 clinical studies in which entecavir was compared with lamivudine are presented in Table 2.

Table 2: Selected Clinical Adverse Events [a] of Moderate-Severe Intensity (Grades 2-4) Reported in Four Entecavir Clinical Trials through 2 Years

Body System/ Adverse Event	Nucleoside-Naive [b]		Lamivudine-Refractory [c]	
	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 Event [a]	15%	18%	22%	23%
Gastrointestinal				
Diarrhea	<1%	0	1%	0
Dyspepsia	<1%	<1%	1%	0
Nausea	<1%	<1%	<1%	2%
Vomiting	<1%	<1%	<1%	0
General				
Fatigue	1%	1%	3%	3%
Nervous System				
Headache	2%	2%	4%	1%
Dizziness	<1%	<1%	0	1%
Somnolence	<1%	<1%	0	0
Psychiatric				
Insomnia	<1%	<1%	0	<1%

[a] Including events of possible, probable, certain, or unknown relationship to treatment regimen.

[b] Studies AI463022 and AI463027.

[c] Including studies AI463026 and AI463014, study AI463014 is a multinational, randomized, double-blind phase II study of three doses of Entecavir (0.1, 0.5 and 1.0mg) versus continued lamivudine 100mg once daily for up to 52 weeks in subjects who experienced recurrent viremia on lamivudine therapy.

Overseas Laboratory Abnormalities

Frequencies of selected treatment-emergent laboratory abnormalities reported during therapy in four clinical trials of entecavir compared with lamivudine are listed in table 3.

Table 3: Selected Treatment-Emergent [a] Laboratory Abnormalities Reported in Four Entecavir Clinical Trials through 2 Years

Test	Nucleoside-Naive [b]		Lamivudine- Refractory [c]	
	Entecavir 0.5 mg n=679	Lamivudine 100 mg n =668	Entecavir 1.0 mg n=183	Lamivudine 100 mg n =190
Any Grade3~4 Laboratory abnormality [d]	35%	36%	37%	45%
ALT>10xULN and >2×baseline	2%	4%	2%	11%
ALT>5.0×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>3.0×ULN	0	0	0	0
Confirmed creatinine increase≥0.5 mg/dl	1%	1%	2%	1%
Hyperglycemia, fasting blood sugar >250 mg/ dl	2%	1%	3%	1%
Glycosuria[e]	4%	3%	4%	6%
Hematuria [f]	9%	10%	9%	6%
Platelets <50,000/mm^3	<1%	<1%	<1%	<1%

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

[b] Studies AI463022 and AI463027.

[c] Including studies AI463026 and AI463014, study AI463014 is a multinational, randomized, double-blind phase II study of three doses of Entecavir (0.1, 0.5 and 1.0mg) versus continued lamivudine 100mg once daily for up to 52 weeks in subjects who experienced recurrent viremia on lamivudine therapy.

[d] Including hematology, routine chemistries, renal and liver function tests, pancreatic enzymes and urinalysis.

[e] Grade 3=3+, large, ≥500mg/dL; Grade 4 =4+, marked, severe.

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

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

Exacerbations of Hepatitis after Discontinuation of Treatment (see WARNINGS)

An exacerbation of hepatitis or ALT flare was defined as ALT>10X ULN and >2X the subject's reference level (minimum of the baseline or last measurement at end of dosing). For all patients who discontinued treatment (regardless of reason), Table 4 presents the cases of patients in each study who experienced post-treatment ALT flares. In these studies, a subset of patients was allowed to discontinue treatment at or after 52 weeks if they achieved a protocol-defined response to therapy. If entecavir is discontinued without regard to treatment response, the rate of post-treatment flares could be higher.

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

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

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

The safety profile of entecavir 1mg (N=51) in HIV/HBV co-infected patients enrolled in study AI463038 was similar to that of placebo (N=17) through 24 weeks of blinded treatment and similar to that seen in non-HIV infected subjects (see **WARNINGS** 3: Co-infection with HIV).

Among the clinical trials conducted in China, the most common adverse events include: ALT elevation, fatigue, dizziness, nausea, bellyache, abdominal discomfort, epigastric pain, hepatic discomfort, myalgia, insomnia and urticaria. Most of the adverse events are mild to moderate. In the comparative study with lamivudine, the incidence rate of the adverse event of this product is similar to that of lamivudine.

CONTRAINDICATIONS

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

WARNINGS

1. Exacerbations of Hepatitis after Discontinuation of Treatment

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 follow-up 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.

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

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

3. Co-infection with HIV

Entecavir has not been evaluated in HIV/HBV co-infected patients who are not simultaneously receiving effective HIV treatment. Limited clinical experience suggests that 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 PHARMACOLOGY AND TOXICOLOGY, Microbiology Antiviral Activity, *Antiviral Activity Against HIV***). Therefore, therapy with entecavir is not recommended for HIV/HBV co-infected patients who are not receiving highly active antiretroviral therapy (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.

PRECAUTIONS

Patients with Renal Impairment

Dosage adjustment of entecavir is recommended for patients with a creatinine clearance <50ml/min, including patients on hemodialysis or CAPD (**see DOSAGE AND ADMINISTRATION**).

Liver Transplant Recipients

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

Four of the 65 subjects received 4 weeks or less of entecavir (2 deaths, 1 retransplantation, and 1 protocol violation) and were not considered evaluable. Of the 61 subjects who received more than 4 weeks of entecavir, 60 received hepatitis B immune globulin post-transplant. Fifty-three subjects (82% of all 65 subjects treated) completed the trial and had HBV DNA measurements at or after 72 weeks treatment post-transplant. All 53 subjects had HBV DNA <50 IU/mL (approximately 300 copies/mL). Eight evaluable subjects did not have HBV DNA data available at 72 weeks, including 3 subjects who died prior to study completion. No subjects had HBV DNA values ≥50 IU/mL while receiving entecavir (plus hepatitis B immune globulin). All 61 evaluable subjects lost HBsAg post-transplant; 2 of these subjects experienced recurrence of measurable HBsAg without recurrence of HBV viremia. This trial was not designed to determine whether addition of entecavir to hepatitis B immune globulin decreased the proportion of subjects with measurable HBV DNA post-transplant compared to hepatitis B immune globulin alone. If entecavir treatment is determined to be necessary for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus, renal function must be carefully monitored both before and during treatment with entecavir. (**see DOSAGE AND ADMINISTRATION** and **PHARMACOKINETICS**).

Information for Patients

Patients should keep under the care of a physician while taking entecavir and they should discuss any new symptoms or concurrent medications with their physician. Patients should be informed that deterioration of liver disease may occur in some cases if treatment is discontinued, and that the regimen should be changed under the direction of the physician.

Patients should be offered HIV antibody testing before starting entecavir therapy. They should be informed that if they have HIV infection and are not receiving effective HIV treatment, entecavir may increase the chance of HIV resistance to HIV medication (**see WARNINGS 3: Co-infection with HIV**).

Patients should be advised that treatment with entecavir has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Therefore appropriate protection measures should be taken.

PREGNANT AND NURSING MOTHERS

There are no adequate studies in pregnant women of entecavir. 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, it can be used during pregnancy only after careful consideration of the risk and benefits.

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

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

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 3,100 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 was seen with entecavir administered orally to rats at exposures >94 times those in humans. Entecavir can be excreted in the milk of rats.

Carcinogenicity

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 1.0mg/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 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 species-specific event. Hepatocellular carcinomas and combined tumors (carcinomas and adenomas) were increased in male mouse at exposures 42 times those in humans. Vascular tumors in female mice (including hemangiomas of ovaries and uterus and hemangiosarcomas of spleen) were increased at exposures 40 times those in human. In rats, hepatocellular adenomas were increased in females at exposures 24 times those in humans; combined tumors (carcinomas and adenomas) 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.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

PEDIATRIC USE

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

GERIATRIC USE

Clinical studies of entecavir did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. No difference has been found between the older patients and younger patients in other clinical trial reports. 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 the renal function should be monitored.

DRUG INTERACTIONS

The metabolism of entecavir was evaluated in vitro and in vivo studies. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system. At concentrations up to approximately 10,000-fold higher than those obtained in humans, entecavir inhibited none of the major human CYP450 enzymes: 1A2, 2C9, 2C19, 2D6, 3A4, 2B6 and 2E1. At concentrations up to approximately 340-fold higher than those observed in human, entecavir did not induce the human CYP450 enzymes: 1A2, 2C9, 2C19, 3A4, 3A5 and 2B6. The pharmacokinetics of entecavir is 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 is 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.

Since entecavir is primarily eliminated by the kidney, 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.

OVERDOSAGE

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

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

PHARMACOLOGY AND TOXICOLOGY

Pharmacological Action

Microbiology

Mechanism of Action

Entecavir, a guanosine nucleoside analogue with activity against hepatitis B virus (HBV) polymerase, is effectively 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 polymerase (reverse transcriptase): (1) base priming of the HBV polymerase; (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand of HBV-DNA. Entecavir triphosphate is a weak inhibitor of cellular DNA polymerases α, β, and δ and mitochondrial DNA polymerase γ with *Ki* values ranging from 18 to over 160 μM.

Antiviral Activity

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

The coadministration of HIV nucleoside reverse transcriptase inhibitors (NRTIs) with entecavir is unlikely to reduce the antiviral efficacy of entecavir against HBV or of any of these agents against HIV. In HBV combination assays in cell culture, abacavir, didanosine, lamivudine, stavudine, tenofovir, or zidovudine were not antagonistic to the anti-HBV activity of entecavir over a wide range of concentrations. In HIV antiviral assays, entecavir was not antagonistic to the cell culture anti-HIV activity of these six NRTIs at >4 times the C_{max} of entecavir.

Antiviral Activity against HIV

A comprehensive analysis of the inhibitory activity of entecavir against a panel of laboratory and clinical human immunodeficiency virus type I (HIV-1) isolates using a variety of cells and assay conditions yielded EC_{50} values ranging from 0.026 to >10μM; the lower EC_{50} values were observed when decreased levels of virus were used in the assay. In cell culture, entecavir selected for an M184 I substitution in HIV reverse transcriptase at micromolar concentrations, confirming inhibitory pressure at high entecavir concentrations. HIV variants containing the M184V substitution showed the loss of susceptibility to entecavir.

Resistance

Cell Culture

The susceptibility of the lamivudine-resistant strains (LVDr) at substitutions of rtM204I/V and rtL180M in the reverse transcriptase region was reduced by 8-fold than that of the wild-type HBV. In combination of other entecavir resistant amino acid substitutions rtT184, rtS202 and/or rtM250, reductions in entecavir susceptibility were also observed in the cell culture. The clinical isolate strains in combination of other substitutions (rtT184A, C, F, G, I, L, M or S; rtS202 C, G or I; and/or rtM250I, L or V) were compared with the wild-type strains, the reductions in entecavir susceptibility were 16-to 741-fold. The virus strains with single appearance of the substitutions at rtT184, rtS202 and rtM250 only had certain influence on the entecavir susceptibility, in more than 1,000 patients with no lamivudine-resistant substitution and no reduction of susceptibility was observed. It was observed in the cell culture that the resistance was mediated by the changing of HBV reverse transcriptase to reduce the competitive binding and the replication capacity of resistant HBV strains was reduced.

Clinical Studies

In the clinical study resistance monitor was conducted for the patients who initially received treatment with 0.5mg of (nucleoside-naive) or 1mg (lamivudine-refractory) of entecavir, at 24th week or after of the treatment and who had HBV-DNA PCR test in the treatment.

Nucleoside-naive Subjects: In the clinical study for the patients with nucleoside-naive treatment, the percentage of the patients with evidence of substitutions genetic test at entecavir resistant rtT184, rt202 and /or rtM250 in the treatment with entecavir up to 144 weeks (see Table 5). Entecavir resistance only occurred when these substitutions occurred on the basis of the lamivudine-resistant sites (rtM204V and rtL180M).

Table 5: Entecavir Genotypic Resistance Occurring for the Nucleoside-naive Patients in the 144-week Study

	1st year	2nd year	3rd year [a]
Number of the Patients with Treatment and Resistance Monitor [b]	663	278	149
Number of the Patients with Entecavir Genotypic Resistance [c]	1 (<1%)	1 (<1%)	1 (<1%)
Cumulative Incidence of the Entecavir Genotypic Resistance [c]	0.2%	0.5%	1.2%
Number of the Patients with Virologic Rebound [d] Caused by Entecavir Resistance [c]	1 (<1%)	0	1(<1%)

[a] The results of 3 years showed that 147 cases among the 149 patients who received 1.0g entecavir treatment in the entecavir continued treatment study and at the same time 130 cases had received the combination therapy of entecavir and lamivudine at the median time of 20 weeks (then received the long-term entecavir treatment).

[b] Patients who had the HBV-DNA PCR test in the treatment at or after the 24th week within the 58 weeks (1st year) of the overall study, between 58th week and 102nd week (2nd year) of the overall study, or between the 102nd week and 156th week of the overall study were included.

[c] The patients had lamivudine-resistant substitutions at the same time.

[d] PCR. HBV-DNA test was increased by ≥1 $\log_{10}$ above nadir, the test value was obtained from the continuous test confirmation or at the end of the time window.

Lamivudine-refractory Subjects:

For the 187 lamivudine-refractory patients with entecavir treatment and resistance monitor, the 10 cases had entecavir resistance substitutions in the baseline virus isolate strains, of 5%, indicated that the previous lamivudine treatment could select these resistance sites which existed with low level before the treatment with entecavir. In the overall study of 144 weeks, 3 cases had virologic rebound among the 10 patients (≥1 $\log_{10}$ increase above nadir). The occurrence of entecavir resistance was summarized in Table 6 for the lamivudine-refractory patients in the overall studies of 144 weeks.

Table 6. Entecavir Genotypic Resistance Occurring for the Lamivudine-refractory Patients in the 144-week Study

	1st year	2nd year	3rd year[a]
Number of the Patients with Treatment and Resistance Monitor [b]	187	146	80
Number of the Patients with Entecavir Genotypic Resistance [c]	11(6%)	12(8%)	15(19%)
Cumulative Incidence of the Entecavir Genotypic Resistance [c]	6%	15%	35%
Number of the Patients with Virologic Rebound [d] Caused by Entecavir Resistance [c]	2(1%)[e]	14 (10%)[e]	13 (16%)[e]

[a] The results of 3 years showed that 48 cases among the 80 patients had received combination therapy of entecavir and lamivudine at the median time of 13 weeks (then received the long-term entecavir treatment).

[b] Patients who had the HBV-DNA PCR test in the treatment at or after the 24th week within the 58 weeks (1st year) of the overall study, between 58th week and 102nd week (2nd year) of the overall study, or between the 102nd week and 156th week of the overall study were included.

[c] The patients had lamivudine-resistant substitutions at the same time.

[d] PCR. HBV-DNA test was increased by ≥1 $\log_{10}$ above nadir, the test value was obtained from the continuous test confirmation or at the end of the time window.

[e] Entecavir resistance occurred at any year; virologic rebound occurred in the specific year in the table.

Cross-resistance

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, entecavir had 8- to 30-fold less inhibition of HBV DNA synthesis for HBV containing lamivudine and telbivudine resistance substitutions rtM204 I / V±rtL180M than for wild-type HBV. Substitutions of rtM204 I / V±rtL180M, rtL80I/V or rtV173L, which are associated with lamivudine and telbivudine resistance, also confer the decreased phenotypic susceptibility to entecavir. 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. The efficacy of entecavir against HBV harboring adefovir resistance-associated substitutions was not 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.

Toxicological Study

Genotoxicity

Entecavir was clastogenic to chromosome fragmentation in 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), 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.

Reproductive Toxicity

In reproductive toxicology studies, in which animals were administered entecavir up to 30 mg/kg for up to 4 weeks, no evidence of impaired fertility was seen in male or female rats at systemic exposures >90 times those achieved in humans at the highest dose of 1.0mg/day. In rodent and dog toxicology studies, seminiferous tubular degeneration was observed at exposures ≥ 35 times those achieved in humans. No testicular change was evident in monkeys.

Reproduction studies have been performed in rats and rabbits at orally administered doses up to 200 and 160 mg/kg/day and showed no embryotoxicity or maternal toxicity at systemic exposures approximately 28 (rats) and 212 (rabbits) times those achieved at the highest recommended dose of 1mg/day in humans. In rats, embryo-fetal 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 3,100 times those in humans. In rabbits, embryo-fetal 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 effect on offspring was seen with entecavir administered orally to rats at exposures >94 times those in humans. Entecavir can be excreted in the milk of rats.

Carcinogenicity

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 1.0mg/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 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 species-specific event. Hepatocellular carcinomas and combined tumors (carcinomas and adenomas) were increased in male mouse at exposures 42 times those in humans. Vascular tumors in female mice (including hemangiomas of ovaries and uterus and hemangiosarcomas of spleen) were increased at exposures 40 times those in human. In rats, hepatocellular adenomas were increased in females at exposures 24 times those in humans; combined tumors (carcinomas and adenomas) 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.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

PHARMACOKINETICS

Absorption

Following oral administration in healthy subjects, entecavir peak plasma concentrations (C_{max}) occurred between 0.5 and 1.5 hours. Steady state was achieved after 6 to 10 days of once-daily administration with approximately 2-fold accumulation.

Effects of food on oral administration

Oral administration of 0.5mg of entecavir with a standard high-fat meal or a light meal resulted in a slight delay in absorption (1.0~1.5 hours fed vs. 0.75 hours fasted), a decrease in C_{max} of 44~46%, and a decrease in AUC of 18~20%. Therefore, entecavir should be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).

Distribution

The pharmacokinetics data show that the estimated apparent volume of distribution is in excess of total body water, suggesting that entecavir is extensively distributed into tissues.

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

Metabolism and Elimination

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

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

Entecavir is predominantly eliminated by the kidney with the clearance rate of 62~73%. Renal clearance is independent of dose and ranges from 360~471mL/min suggesting that entecavir undergoes both glomerular filtration and net tubular secretion.

Special Populations

Gender: There is no significant gender difference in entecavir pharmacokinetics.

Race: There is no significant racial difference in entecavir pharmacokinetics.

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

Renal Impairment

The pharmacokinetics of entecavir following a single 1-mg dose was studied in subjects (without chronic hepatitis B infection) with selected degrees of renal impairment, including subjects whose renal impairment was managed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) showed that the clearance rate was decreased with the reduction of the creatinine 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. Entecavir should be administered after hemodialysis.

Hepatic Impairment

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

Post-liver Transplant:

Limited data are available on the safety and efficacy of entecavir in liver transplant recipients. However, 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 function. The 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. Renal function must be carefully monitored both before and during treatment with entecavir in liver transplant recipients who have received or are receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus. (see Dosage Adjustment for Patients with Renal Impairment, **DOSAGE AND ADMINISTRATION**).

Pediatrics: Pharmacokinetic studies have not been conducted in children.

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