NEW ZEALAND DATA SHEET
ENTECAVIR SANDOZ (ENTECAVIR MONOHYDRATE)

1. PRODUCT NAME

Entecavir Sandoz 0.5 mg film-coated tablet

Entecavir Sandoz 1 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Entecavir Sandoz 0.5 mg film-coated tablet contains 0.5mg entecavir (as monohydrate).

Each Entecavir Sandoz 1 mg film-coated tablet contains 1 mg entecavir (as monohydrate).

Excipient(s) with known effect: Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Entecavir Sandoz 0.5mg film coated tablet – white, round with debossment on both sides, "SZ" on one side and "108" on the other side.

Entecavir Sandoz 1mg film coated tablet – pink, round with debossment on both sides, "SZ" on one side and "109" on the other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Entecavir Sandoz is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults 16 years or older with evidence of active liver inflammation.

This indication is based on histologic, virologic, biochemical and serological responses in nucleoside-treatment naive and lamivudine-resistant adult patients with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease.

4.2. DOSE AND METHOD OF ADMINISTRATION

Recommended Dosage

Entecavir Sandoz should be taken orally, on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).

The recommended oral dose of Entecavir Sandoz in adults and adolescents older than 16 years is 0.5 mg once daily. For lamivudine-refractory patients [history of hepatitis B viraemia while receiving lamivudine therapy or known lamivudine resistance (LVD^R commonly called YMDD mutations)], the recommended dose is 1 mg once daily (or alternatively 2 tablets of 0.5 mg once daily).

Renal Impairment

In patients with renal impairment, the apparent oral clearance of entecavir monohydrate decreased as creatinine clearance decreased (see Section 5.2 Pharmacokinetic properties – Special Populations: Renal impairment). Dosage adjustment of entecavir is recommended for

patients with creatinine clearance < 50 mL/min, including patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in Table 1.

Table 1. Recommended dosage of entecavir in patients with renal impairment

Creatinine Clearance (mL/min)	Nucleoside-Naïve	Lamivudine-Refractory
≥ 50	0.5 mg once daily	1.0 mg once daily
30 to < 50	0.25 mg once daily* **or** 0.5 mg every 48 hours	0.5 mg once daily **or** 1.0 mg every 48 hours
10 to < 30	0.15 mg once daily* **or** 0.5 mg every 72 hours	0.3 mg once daily* **or** 1.0 mg every 72 hours
< 10	0.05 mg once daily* **or** 0.5 mg every 5-7 days	0.1 mg once daily* **or** 1.0 mg every 5-7 days
Haemodialysis or CAPD **	0.05 mg once daily* **or** 0.5 mg every 5-7 days	0.1 mg once daily* **or** 1.0 mg every 5-7 days

* For doses < 0.5mg entecavir oral solution is recommended. Do not split tablets.
** On haemodialysis days, administer after haemodialysis

Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

Duration of Therapy

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

4.3. CONTRAINDICATIONS

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

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Co-infection with HIV

Entecavir has not been evaluated in HIV/HBV co-infected patients not simultaneously receiving HIV treatment. Therapy with entecavir monohydrate is not recommended for human immunodeficiency virus (HIV)/HBV co-infected patients who are not receiving highly active antiretroviral therapy. There is a potential for the development of HIV resistance if entecavir monohydrate is used to treat chronic hepatitis B infection in patients with untreated HIV infection.

Lactic Acidosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals.

Exacerbations of Hepatitis after Discontinuation of Treatment

Acute exacerbation of hepatitis has been reported in patients who have discontinued hepatitis B therapy, including therapy with entecavir (see Section 4.8 Undesirable effects). The majority of post-treatment exacerbations appear to be self-limited. However, severe exacerbations,

including fatalities, may occur. The causal relationship of these events to discontinuation of therapy is unknown. Hepatic function should be monitored closely for at least several months after discontinuation. If appropriate, resumption of hepatitis B therapy may be warranted.

Patients with Renal Impairment

Dosage adjustment of entecavir is recommended for patients with renal impairment who have creatinine clearance < 50 mL/min (see Section 4.2 Dose and method of administration – Renal Impairment).

Liver Transplant Recipients

Limited data are available on the safety and efficacy of entecavir in liver transplant recipients. In a single-arm, open-label study, patients who had HBV DNA less than 172 IU/mL at the time of transplant were treated with entecavir 1 mg once daily post-transplant. On treatment, 15 subjects (23%) had liver-related adverse events of interest: fourteen subjects had ascites (22%) and 1 subject each had bacterial peritonitis, hepatic encephalopathy, and recurrent hepatocellular carcinoma (HCC). In 12 of the 15 subjects, all liver-related events occurred during the first 30 days post-transplant, and were considered post-operative complications. During the first 30 days post-transplant, 18 of 65 treated subjects (28%) or 8 of 61 evaluable subjects (13%) had episodes of acute liver rejection with 1 subject who required re-transplantation. None of the 61 evaluable patients had virologic recurrence. The frequency and nature of adverse events and acute liver rejection in this study were consistent with those expected in patients who have received a liver transplant and the known safety profile of entecavir. (See Section 5.1 Pharmacodynamic properties – Clinical Trials)

Renal function should be carefully monitored before and during entecavir therapy in liver transplant recipients receiving an immunosuppressant that may affect renal function such as cyclosporine or tacrolimus (see Section 4.2 Dose and method of administration – Hepatic Impairment and 5.2 Pharmacokinetic properties – Hepatic Impairment and Post-liver transplant).

Decompensated Liver Disease

A study of entecavir at a dose of 1 mg once daily has been conducted in patients with decompensated liver disease (see Section 5.1 Pharmacodynamic properties – Clinical Trials and 4.8 Undesirable effects).

Co-infection with Hepatitis C or D

There are no data on the efficacy of entecavir in patients co-infected with hepatitis C or D.

Lactose

This medicinal product contains 120.5 mg of lactose in each 0.5 mg daily dose and 241 mg of lactose in each 1 mg daily dose. Entecavir monohydrate tablets should be used with caution in patients with lactose intolerance.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine.

Patient Information

A Consumer Medicine Information Leaflet for entecavir is available for patient information.

Patients should remain under the care of a physician while taking entecavir. They should discuss any new symptoms or concurrent medications with their physician.

Patients should be advised to take entecavir on an empty stomach (at least 2 hours before and at least 2 hours after a meal).

Patients should be informed that deterioration of liver disease may occur in some cases if treatment is discontinued, and that they should discuss any change in regimen with their physician.

Patients should be advised that treatment with entecavir has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination (see Section 4.6 Fertility, pregnancy and lactation – Use in Pregnancy).

Paediatric Use

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

Geriatric Use

Clinical studies of entecavir did not include sufficient numbers of participants aged 65 years and over to determine whether they respond differently from younger participants. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Entecavir monohydrate 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 Section 4.2 Dose and method of administration – Renal Impairment)

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicinal Products

Since entecavir monohydrate is predominantly eliminated by the kidney (see Section 5.2 Pharmacokinetic properties – Excretion), co-administration with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of either medicinal product. Co-administration of entecavir monohydrate with either lamivudine, adefovir dipivoxil or tenofovir disoproxil fumarate resulted in no significant drug interactions. The effects of co-administration of entecavir monohydrate with other medicinal products that are excreted renally or affect renal function have not been evaluated. Patients should be monitored closely for adverse events when entecavir is coadministered with such medicinal products.

Food

Administration of entecavir with food decreased absorption (see Sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties – Absorption).

4.6. FERTILITY, PREGNANCY AND LACTATION

Fertility

Toxicology studies in animals administered entecavir have shown no evidence of impaired fertility (see Section 5.3 Preclinical safety data – Impairment of Fertility).

Labour and delivery

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

Use in pregnancy

Category B3

There are no adequate and well-controlled studies in pregnant women. Entecavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

To monitor maternal-fetal outcomes of pregnant women exposed to entecavir monohydrate, physicians are encouraged to report all patients taking Entecavir Sandoz during pregnancy to Novartis by calling 0800 354 335.

Use in lactation

Entecavir monohydrate and/or its conjugate metabolites are excreted in the milk of rats. It is not known whether excretion occurs in human milk. Mothers should be instructed not to breastfeed if they are taking entecavir.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and operate machinery were not assessed as part of its registration. Dizziness, fatigue and somnolence are common side effects which may impair the ability to drive and use machines.

4.8. UNDESIRABLE EFFECTS

Assessment of adverse reactions is based on four clinical studies in which 1720 patients with chronic HBV infection received double-blind treatment with entecavir 0.5 mg/day (n = 679), entecavir 1 mg/day (n = 183), or lamivudine (n = 858) for up to 107 weeks. The safety profiles of entecavir and lamivudine were comparable in these studies. Among entecavir-treated patients, the most common adverse events of any severity with at least a possible relation to entecavir were headache (9%), fatigue (6%), dizziness (4%) and nausea (3%).

In these clinical studies, the 594 entecavir monohydrate-treated patients who received blinded therapy for more than 52 weeks reported adverse reactions similar in nature and severity to those reported during the first 52 weeks of treatment.

Clinical Trials Adverse Events

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

Table 2. Selected clinical adverse events[a] of moderate-severe intensity (Grades 2-4) reported in four entecavir monohydrate clinical trials

Body System/ Adverse Event	Entecavir 0.5 mg n=679	Lamivudine 100mg n=668	Entecavir 1 mg n=183	Lamivudine 100mg n=190
Gastrointestinal				
Diarrhea	< 1%	0	1%	0
Dyspepsia	< 1%	< 1%	1%	0
Nausea	< 1%	< 1%	< 1%	2%
Vomiting	< 1%	< 1%	< 1%	0
General				
Fatigue	1%	1%	3%	3%
Nervous System				
Headache	2%	2%	4%	1%
Dizziness	< 1%	< 1%	0	1%
Somnolence	< 1%	< 1%	0	0
Psychiatric				
Insomnia	< 1%	< 1%	0	< 1%

[a] Includes events of possible, probable, certain or unknown relationship to treatment regimen.
[b] Studies AI463022 and AI463027.
[c] Includes Study AI463206 and the entecavir 1mg and lamivudine treatment arms of Study AI463014, a Phase 2 multinational, randomised, 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 patients who experienced recurrent viraemia on lamivudine therapy.

Laboratory Findings

Table 3 shows laboratory findings from four double-blind, lamivudine-controlled clinical studies in which 679 nucleoside-naïve patients received entecavir 0.5 mg once daily for a median of 53 weeks and 183 lamivudine-refractory patients received entecavir 1 mg for a median of 69 weeks.

Table 3. Selected laboratory abnormalities reported during treatment in four clinical trials

	Nucleoside-Naïve[a]	Lamivudine-Refractory[b]
	Entecavir 0.5 mg	**Entecavir 1 mg**
Test	n=679	n=183
ALT > 10 X ULN and > 2 X baseline	2%	2%
ALT > 3 X baseline	5%	4%
ALT > 2 X baseline and **total bilirubin** > 2 X ULN and >2 X baseline	< 1%	< 1%
Albumin < 2.5 g/dL	< 1%	0
Amylase > 3 X baseline	2%	2%
Lipase > 3 X baseline	12%	18%
Platelets < 50,000/mm^3	< 1%	< 1%

[a] Median duration of therapy was 53 weeks
[b] Median duration of therapy was 69 weeks

ULN=upper limit of normal.

Among entecavir-treated patients in these studies, on-treatment alanine aminotransferase (ALT) elevations > 10 X ULN and > 2 X baseline generally resolved with continued treatment. A majority of these exacerbations were associated with a > 2 log10/mL reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

ALT Flares after Discontinuation of Treatment

Acute exacerbations of hepatitis have been reported in patients who have discontinued anti-HBV therapy, including therapy with entecavir (see Section 4.4 Special warnings and precautions for use). The frequency of exacerbations of hepatitis or ALT flare (defined as ALT > 10 X ULN and 2 X the patient's reference level) during off-treatment follow-up in clinical studies with entecavir is presented in Table 4.

Table 4. ALT flares during off-treatment follow-up in Studies AI463022, AI463026 and AI463027

	Patients with ALT Elevations > 10 X ULN and > 2 X Reference[a]	
	Entecavir	**Lamivudine**
Nucleoside-naive	28/476 (6%)	43/417 (10%)
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 patients and 10 weeks for lamivudine-treated patients.

Patients with Decompensated Liver Disease

Clinical adverse reactions observed through Week 48 in Study AI463048 in which entecavir 1 mg once daily was compared with adefovir dipivoxil in patients with chronic hepatitis B infection and decompensated liver disease are listed in Table 5. The cumulative rates of discontinuation for adverse events and on-study cumulative rates of death and HCC are also shown in Table 5.

Table 5. Selected safety outcomes in Study AI463048

	Entecavir 1 mg n=102	**Adefovir dipivoxil 10 mg n=89**
Clinical Adverse Events[a] of Moderate-Severe Intensity (grades 2-4) Through Week 48		
Body System/ Adverse Event		
Gastrointestinal Disorders		
Vomiting	< 1%	1%
Diarrhea	0	1%
Investigations		
Blood bicarbonate decreased	2%	0
Nervous System Disorders		
Dizziness	2%	0
Headache	0	1%
Renal and Urinary Disorders		
Renal failure	<1%	2%
General Disorders and Administration Site		

	Entecavir 1 mg n=102	Adefovir dipivoxil 10 mg n=89
Conditions		
Fatigue	<1%	1%
Discontinuation for Adverse Event (cumulative)	7%	6%
Deaths (cumulative)	23%	33%
HCC (cumulative)	12%	20%

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

Causes of death in Study AI463048 were generally liver-related, as expected in this population. The time to onset of HCC or death (whichever occurred first) was comparable in the two treatment groups.

Laboratory test abnormalities reported through week 48 in study AI463048 are listed in Table 6.

Table 6. Selected laboratory abnormalities reported through week 48 in Study AI463048

Test	Entecavir 1 mg n=102
ALT > 10 X ULN and > 2 X baseline	0
ALT > 2 X baseline and **total bilirubin** > 2 X ULN and > 2 X baseline	1%
Albumin < 2.5 g/dL	30%
Lipase > 3 X baseline	10%
Platelets < 50,000/mm^3	20%

ULN = upper limit of normal

Patients Co-infected with HIV

Patients co-infected with HBV and HIV who experienced recurrence of HBV viremia while receiving a lamivudine-containing highly active antiretroviral regimen were treated with their lamivudine-containing regimen (lamivudine dose, 300 mg/day) and either entecavir 1 mg once daily or placebo. After 24 weeks of double-blind therapy and a mean of 17 weeks of open-label therapy (where all patients received entecavir), the adverse event and laboratory abnormality profiles were similar for the entecavir and placebo treatment groups. Entecavir has not been evaluated in HIV/HBV co-infected patients who are not concurrently receiving effective HIV treatment (see Section 4.4 Special warnings and precautions for use – Co-infection with HIV).

Post-marketing Experience

The following events have been identified during post approval use of entecavir. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Immune system disorders:	anaphylactoid reaction
Skin and subcutaneous tissue disorders:	alopecia, rash.
Hepatobiliary disorders:	increased transaminases.

Metabolism and nutrition disorders:	Lactic acidosis, often in association with hepatic decompensation, other serious medical conditions or drug exposures. Patients with decompensated cirrhosis may be at higher risk for lactic acidosis.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9. OVERDOSE

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

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors ATC code: J05AF10.

Mechanism of action

Entecavir monohydrate is a guanosine nucleoside analogue with activity against HBV polymerase. It is phosphorylated to the active triphosphate (TP) form, which has an intracellular half-life of 15 hours. Intracellular TP levels are directly related to extracellular entecavir monohydrate concentrations, with no significant accumulation beyond initial plateau levels. By competing with the natural substrate deoxyguanosine-TP, entecavir monohydrate-TP inhibits all 3 functional activities of the viral polymerase: (1) 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 monohydrate-TP K_i value for inhibition of HBV DNA polymerase is 1.2 nM. Entecavir monohydrate-TP is a weak inhibitor of cellular DNA polymerases α, β, δ and ε with K_i values of 18 to 40 μM. It did not inhibit mitochondrial γ polymerase (K_i > 160μM) and did not affect the mitochondrial DNA content of human hepatoma cells *in vitro.* Entecavir monohydrate inhibited HBV DNA synthesis at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. IC_{50} values for entecavir monohydrate against lamivudine-resistant HBV ranged from 0.029-0.061 μM.

Resistance *in vitro*

There was reduced susceptibility to entecavir monohydrate when LVD^R substitutions (M204I/V ± L180M) were present. Entecavir monohydrate inhibited the replication of LVD^R

HBV at 8-fold higher concentrations than that for the wild-type virus in cell-based studies. At extracellular concentrations representative of plasma levels achieved with 1 mg dosing, intracellular entecavir monohydrate-TP levels would be expected to surpass those needed to inhibit the enzyme activity of lamivudine-resistant HBV polymerases. Recombinant viruses encoding adefovir-resistant substitutions at either rtN236T or rtA181V remained fully susceptible to entecavir monohydrate.

Lamivudine-resistant strains harboring rtL180M plus rtM204V in combination with amino acid substitution rtA181C conferred 16- to 122-fold reductions in entecavir phenotypic susceptibility.

Clinical resistance

Genotyping was performed on paired baseline and on-treatment samples from all continuously treated patients with polymerase chain reaction (PCR)-detectable HBV DNA (≥ 300 copies/mL) at Week 48, 96, 144, 192 and 240 or at the end of dosing to identify any novel or known resistance substitutions that emerged during entecavir therapy. Virologic breakthrough (≥ 1 $\log_{10}$ increase above nadir in HBV DNA by PCR) due to resistance to entecavir monohydrate requires the existence of primary lamivudine resistance substitutions (M204I/V ± L180M) along with an additional substitution at residues T184, S202, and/or M250 of the polymerase protein.

Nucleoside naïve studies

Patients in nucleoside-naïve studies received 0.5 mg entecavir monohydrate for up to 96 weeks (see Section 5.1 Pharmacodynamic properties – Clinical Trials). Study participants who failed to achieve the study-defined complete response by Week 96 were offered continued entecavir monohydrate treatment in a rollover study. Complete response for HBeAg positive was < 0.7 MEq/mL (approximately 7 x 10^5 copies/mL) serum HBV DNA and HBeAg loss and, for HBeAg negative, was < 0.7 MEq/mL HBV DNA and ALT normalisation.

By week 96, evidence of emerging amino acid substitution rtS202G with rtM204V and rtL180M was detected in the HBV of 2 subjects and 1 of them experienced virologic rebound (≥ 1 $\log_{10}$ increased above nadir). In addition, emerging amino acid substitution at rtM204I/V and rtL180M, rtL80I or rtV173L, which conferred decreased phenotypic susceptibility to entecavir in the absence of rtT184, rtS202 or rtM250 changes, were detected in the HBV of 3 subjects who experienced virologic rebound.

Results in Table 7reflect use of a 1 mg dose of entecavir monohydrate for 147 of 149 patients in Year 3 and 121 patients in Year 4, 108 patients in Year 5 and of combination entecavir monohydrate plus lamivudine therapy (followed by long-term entecavir monohydrate monotherapy) for a median of 20 weeks for 130 of 149 patients in Year 3 and for 1 week for 1 of 121 patients in Year 4 in the rollover study. Through Week 240 in nucleoside-naive studies, genotypic evidence of ETVr substitutions at rtT184, rtS202, or rtM250 was identified in 3 patients treated with entecavir monohydrate, 2 of whom experienced virologic breakthrough (see Table 7). These substitutions were observed only in the presence of LVD^R substitutions (rtM204Vand rtL180M).

Table 7. Genotypic Resistance to Week 240, Nucleoside-Naïve Patients

	Year 1	Year 2	Year 3[a]	Year 4[a]	Year 5[a]
Patients treated and monitored for resistance[b]	663	278	149	121	108
Patients in specific year with:					
Emerging genotypic entecavir resistance[c]	1	1	1	0	0
genotypic entecavir resistance[c] with virologic breakthrough[d]	1	0	1	0	0
Cumulative probability of:					
emerging genotypic entecavir resistance[c]	0.2%	0.5%	1.2%	1.2%	1.2%
genotypic entecavir resistance[c] with virologic breakthrough[d]	0.2%	0.2%	0.8%	0.8%	0.8%

[a] Results reflect use of a 1 mg dose of entecavir monohydrate for 147 patients in Year 3 and all patients in Years 4 and 5 and of combination of entecavir monohydrate-lamivudine therapy (followed by long-term entecavir therapy) for a median of 20 weeks for 130 patients in Year 3 and for 1 week for 1 patient in Year 4 in a rollover study.

[b] Includes patients 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), after Week 102 through Week 156 (year 3), after week 156 through week 204 (Year 4), or after week 204 through week 252 (Year 5).

[c] Entecavir monohydrate resistance substitutions at residues rtT184, rtS202, or rtM250. Patients also have lamivudine resistance substitutions (rtM204V and rtL180M).

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

Lamivudine-refractory studies

Participants treated with entecavir monohydrate 1 mg once daily in lamivudine-refractory studies (see Section 5.1 Pharmacodynamic properties – Clinical Trials who failed to achieve the study-defined complete response by Week 96 were offered continued entecavir treatment in a rollover study. Participants received 1 mg entecavir once daily for up to an additional 96 weeks. Genotypic analysis of clinical samples from lamivudine-refractory patients identified emerging entecavir resistance substitutions in 11/187 patients in Year 1, 12/146 patients in Year 2, 16/80 patients in Year 3, 6/52 patients in Year 4 and 2/33 patients in Year 5 (see Table 8). Results in Table 8 reflect the use of combination entecavir monohydrate plus lamivudine therapy (followed by long-term entecavir monohydrate monotherapy) for a median of 13 weeks for 48 of 80 patients in Year 3, for a median of 38 weeks for 10 of 52 patients in Year 4 and for 16 weeks for 1 of 33 patients in Year 5 in the rollover study. The presence of entecavir resistance substitutions at baseline in isolates from 10 (5%) of 187 lamivudine-refractory patients indicates that prior lamivudine treatment can select these resistance substitutions and that they can exist at a low frequency before entecavir monohydrate treatment. Three of the 10 patients experienced virologic breakthrough (≥ log10 increase above nadir) in the 240 weeks of follow-up. Emerging entecavir resistance in lamivudine-refractory studies through Week 240 is summarised in Table 8.

Table 8. Genotypic Entecavir Resistance to Week 240, Lamivudine-Refractory Patients

	Year 1	Year 2	Year 3[a]	Year 4[a]	Year 5[a]
Patients treated and monitored for resistance[b]	187	146	80	52	33
Patients in specific year with:					
Emerging genotypic entecavir resistance[c]	11	12	16	6	2
Genotypic entecavir resistance[c] with virologic breakthrough[d]	2[e]	14[e]	13[e]	9[e]	1[e]
Cumulative probability of:					

	Year 1	Year 2	Year 3[a]	Year 4[a]	Year 5[a]
Emerging genotypic entecavir resistance[c]	6%	15%	36%	47%	51%
Genotypic entecavir resistance[c] with virologic breakthrough[d]	1%[e]	11%[e]	27%[e]	41%[e]	44%[e]

[a] Results reflect use of combination entecavir-lamivudine therapy (followed by long-term entecavir therapy) for a median of 13 weeks for 48 patients in Year 3, a median of 38 weeks for 10 patients in Year 4, and for 16 weeks in 1 patient in Year 5 in a rollover study.

[b] Includes patients 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), after week 102 through week 156 (Year 3), after week 156 through week 204 (Year 4), or after week 204 through week 252 (Year 5).

[c] Entecavir resistance substitutions at residues rtT184, rtS202, or rtM250. Patients also had lamivudine resistance substitutions (rtM204V/I ± rtL180M).

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

[e] Entecavir resistance substitutions occurring in any year; virologic breakthrough in specified year.

Integrated Analysis of Phase 2 and 3 Clinical studies – in a post-approval integrated analysis of entecavir resistance data from 17 Phase 2 and 3 clinical studies, an emergent entecavir resistance-associated substitution rtA181C was detected in 5 out of 1461 subjects during treatment with entecavir. This substitution was detected only in the presence of lamivudine resistance-associated substitutions rtL180M plus rtM204V.

Clinical trials

The safety and efficacy of entecavir were evaluated in four active-controlled trials on five continents. These studies included 1720 patients 16 years of age or older with chronic hepatitis B infection (serum HBsAg-positive for at least 6 months) accompanied by evidence of viral replication (detectable serum HBV DNA, as measured by the bDNA hybridisation or PCR assay). Subjects in Phase 3 studies AI463022, AI 463026 and AI463027 had persistently elevated ALT levels ≥ 1.3 times ULN and chronic inflammation on liver biopsy compatible with a diagnosis of chronic viral hepatitis, whereas abnormal ALT was not an entry criterion and liver biopsy was optional in the Phase 2 Study AI463014. The safety and efficacy of entecavir were also evaluated in an active-controlled study of 191 HBV-infected patients with decompensated liver disease and in a study of 68 patients co-infected with HBV and HIV.

Nucleoside-Naïve Patients with Compensated Liver Disease

HBeAg-positive

Study AI463022 was a multinational, randomised, double-blind study of entecavir 0.5 mg once daily versus lamivudine 100 mg once daily for 52 weeks in 709 (of 715 randomised) nucleoside-naïve patients with chronic hepatitis B infection and detectable HBeAg. The mean age of patients was 35 years (range 16 to 78), and 75% were male; 57% were Asian, 40% were Caucasian, and 13% had previously received interferon-α treatment. At baseline, patients had a mean Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA level as measured by Roche COBAS Amplicor® PCR assay of 9.66 $\log_{10}$ copies/mL, and mean serum ALT level of 143 U/L. Paired adequate liver biopsy samples were collected for 89% of patients.

HBeAg-negative (anti-HBe positive/HBV DNA positive)

Study AI463027 was a multinational, randomised, double-blind study of entecavir 0.5 mg once daily versus lamivudine 100 mg once daily for 52 weeks in 638 (of 648 randomised) nucleoside-naïve patients with HBeAg-negative (HBeAb-positive) chronic hepatitis B

infection (presumed to have pre-core or core-promoter mutants). The mean age of patients was 44 years (range 18 to 77), and 76% were male. Thirty-nine percent were Asian and 58% were Caucasian; 13% had previously received interferon-α treatment. At baseline, patients had a mean Knodell Necroinflammatory Score of 7.8, mean serum HBV DNA level as measured by Roche COBAS Amplicor PCR assay of 7.58 $\log_{10}$ copies/mL, and mean serum ALT level of 141.7 U/L. Ninety-eight percent of patients had a baseline liver biopsy, and 89% had a biopsy at Week 48; paired samples were collected for 88% of patients. Response was assessed at Week 52 based on test results obtained at the Week 48 visit.

In Studies AI463022 and AI463027, entecavir was superior to lamivudine on the primary efficacy endpoint of Histologic Improvement, defined as ≥ 2-point reduction in Knodell Necroinflammatory Score with no worsening in Knodell Fibrosis Score at Week 48. Histologic Improvement and change in Ishak Fibrosis Score are shown in Table 9. Biochemical, virologic, and serologic outcome measures are shown in Table 10.

Table 9. Histologic improvement and change in ishak fibrosis score at Week 48, Nucleoside-Naive Patients in Studies AI463022 and AI463027

	Study AI463022 (HBeAg-Positive)			**Study AI463027 (HBeAg-Negative)**		
	Entecavir 0.5 mg	**Lami-vudine 100 mg**	**Difference Entecavir-Lamivudine (95% CI)[b]**	**Entecavir 0.5 mg**	**Lami-vudine 100 mg**	**Difference Entecavir-Lamivudine (95% CI)[b]**
	n=314[a]	**n=314[a]**		**n=296[a]**	**n=287[a]**	
Histologic Improvement (Knodell Scores)						
Improvement[c]	72%	62%	9.9%[d] (2.6%, 17.2%)	70%	61%	9.6%[e] (2.0%, 17.3%)
No improvement	21%	24%		19%	26%	
Ishak Fibrosis Score[f]						
Improvement[f]	39%	35%	3.2%[g] (-4.4%, 10.7%)	36%	38%	-1.8%[g] (-9.7%, 6.0%)
No change	46%	40%		41%	34%	
Worsening[f]	8%	10%		12%	15%	
Missing week 48 biopsy	7%	14%		10%	13%	

[a] Patients with evaluable baseline histology (baseline Knodell Necroinflammatory Score ≥ 2)

[b] In these analyses, missing or inadequate biopsies at Week 48 were classified "no improvement"

[c] ≥ 2-point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.

[d] $p<0.01$

[e] $p<0.05$

[f] For Ishak Fibrosis Score, improvement = ≥ 1-point decrease from baseline and worsening = ≥ 1-point increase from baseline

[g] Not significant

CI = confidence interval

Table 10. Biochemical, virologic, and serologic endpoints at Week 48, Nucleoside-Naïve Patients in Studies AI463022 and AI463027

	Study AI463022 (HBeAg-Positive)			Study AI463027 (HBeAg-Negative)		
	Entecavir 0.5 mg	**Lamivudine 100 mg**	**Difference Entecavir-Lamivudine (95% CI)**	**Entecavir 0.5 mg**	**Lamivudine 100 mg**	**Difference Entecavir-Lamivudine (95% CI)**
	n=354	**n=355**		**n=325**	**n=313**	
ALT normalisation (≤ 1 X ULN)	68%	60%	8.4%[a] (1.3%, 15.4%)	78%	71%	6.9%[a] (0.2%, 13.7%)
HBV DNA						
Mean change from baseline by PCR[b] (log_{10} copies/mL)	-6.86	-5.39	-1.52[c] (-1.8, -1.3)	-5.04	-4.53	-0.43[c] (-0.6, -0.3)
Proportion undetectable (<300 copies/mL) by PCR[b,d]	67%	36%	30.3%[c] (23.3%, 37.3%)	90%	72%	18.3%[c] (12.3%, 24.2%)
<0.7 MEq/mL by bDNA[e]	91%	65%	25.6%[c] (19.8%, 31.4%)	95%	89%	5.9[f] (1.8%, 10.1%)
Loss of HBeAg	22%	20%		N/A	N/A	
HBeAg seroconversion	21%	18%		N/A	N/A	

[a] $p<0.05$.

[b] Roche COBAS Amplicor PCR assay.

[c] $p<0.0001$.

[d] At Week 24, HBV DNA < 300 copies/mL by PCR was observed in 42% of entecavir-treated patients and 25% of lamivudine-treated patients ($p<0.0001$) in Study AI463022 and 74% of entecavir-treated patients and 62% of lamivudine-treated patients ($p=0.0013$) in Study AI463027.

[e] Quantiplex bDNA assay.

[f] $p<0.01$.

CI = confidence interval

Responses for patients with baseline Knodell Fibrosis Scores of 4 (cirrhosis) were comparable to overall responses on all efficacy outcome measures (all patients had compensated liver disease). Histologic Improvement was independent of baseline HBV DNA or ALT levels.

Covalently closed circular deoxyribonucleic acid (cccDNA) is a stable genomic form of nuclear HBV DNA that serves as an hepatic reservoir of virus, provides the template for HBV transcription, and contributes to viral persistence and relapse. For a subset of patients with paired liver samples in Study AI463022, the mean change from baseline in hepatic cccDNA at Week 48 was -0.9 log_{10} copies/human genome equivalents (HGEq) (approximately 8-fold reduction) for entecavir-treated patients (n=159) and -0.7 log_{10} copies/HGEq (approximately 5-fold reduction) for lamivudine-treated patients (n=146). In Study AI463027, the mean change from baseline in hepatic cccDNA at Week 48 was -0.5 log_{10} copies/HGEq (approximately 3-fold reduction) in each treatment group (n=107 for entecavir-treated patients and n=104 for lamivudine-treated patients).

Outcomes beyond 48 Weeks

HBeAg-positive

Through 96 weeks, cumulative confirmed outcomes for HBeAg-positive patients (all treated) demonstrate that continued treatment with entecavir (n=354) resulted in an increase in the proportion of patients with HBV DNA < 300 copies/mL by PCR (80%) and ALT normalization (≤ 1 times ULN) (87%). Through the last observation on or off treatment, 31% of entecavir-treated patients had HBeAg seroconversion and 5% had HBsAg loss. In the lamivudine treatment group (n=355), cumulative confirmed HBV DNA < 300 copies/mL by PCR occurred in 39% of patients and ALT normalization in 79%; 26% of patients had HBeAg seroconversion and 3% had HBsAg loss. The difference between treatment groups was statistically significant for percentage of patients with HBV DNA < 300 copies/mL and ALT normalization ($p < 0.01$).

At end of dosing, among patients who continued treatment beyond 52 weeks (median of 96 weeks), 74% of 243 entecavir-treated and 37% of 164 lamivudine-treated patients had HBV DNA < 300 copies/mL by PCR while ALT normalization (≤ 1 times ULN) occurred in 79% of entecavir -treated and 68% of lamivudine-treated patients.

HBeAg-negative

Through 96 weeks for HBeAg-negative patients, 94% of entecavir-treated patients (n=325) and 77% of lamivudine-treated patients (n=313) had cumulative confirmed HBV DNA < 300 copies/mL ($p<0.01$). ALT normalization (≤ 1 times ULN) occurred in 89% of entecavir-treated patients and 84% of lamivudine-treated patients.

For 26 entecavir-treated and 28 lamivudine-treated patients who continued treatment beyond 52 weeks (median 96 weeks), 85% of entecavir-treated and 57% of lamivudine-treated patients had HBV DNA < 300 copies/mL by PCR at end of dosing. ALT normalization (≤ 1 times ULN) occurred in 27% of entecavir-treated and 21% of lamivudine-treated patients at end of dosing.

Liver biopsy results: Of the 679 entecavir monohydrate-treated patients in the two nucleoside-naïve studies, 293 (43%) eligible patients enrolled in a long-term rollover study and continued entecavir monohydrate therapy. Patients in the rollover study received entecavir monohydrate 1 mg once daily. Sixty-nine of the 293 patients elected to have a repeat liver biopsy after a total treatment duration of more than 144 weeks (3 years). Fifty-seven patients had both an evaluable baseline and long-term biopsy, with a median duration of entecavir monohydrate therapy of 280 weeks (approximately 6 years). Ninety-six percent of these patients had Histologic Improvement (a ≥ 2-point decrease in Knodell necroinflammatory score from baseline with no worsening of the Knodell fibrosis score), and 88% had a ≥ 1-point decrease in Ishak fibrosis score. Of the 43 patients with a baseline Ishak fibrosis score of ≥ 2, 58% had a ≥ 2 point decrease. All (10/10) patients with advanced fibrosis or cirrhosis at baseline (Ishak fibrosis score of 4, 5 or 6) had a ≥ 1 point decrease (median decrease from baseline of 1.5 points). At the time of the long-term biopsy, 57 (100%) of patients had HBV DNA < 300 copies/mL and 49 (86%) had serum ALT ≤1 X ULN.

Lamivudine refractory patients

Study AI463026 was a multinational, randomised, double-blind study of entecavir in 286 (of 293 randomised) patients with lamivudine-refractory chronic hepatitis B infection. Patients receiving lamivudine at study entry either switched to entecavir 1 mg once daily or continued on lamivudine 100 mg for 52 weeks. The mean age of patients was 39 years (range 16 to 74), and 76% were male; 37% were Asian and 62% were Caucasian. Eighty-five percent had LVD^R

mutations at baseline. Patients had a mean Knodell Necroinflammatory Score of 6.5, mean serum HBV DNA level as measured by Roche COBAS Amplicor PCR assay of 9.36 $\log_{10}$ copies/mL, and mean serum ALT level of 128 U/L. Response was assessed at Week 52 based on test results obtained at the Week 48 visit. Ninety-eight percent of patients had a baseline liver biopsy, and 88% had a biopsy at Week 48; paired samples were collected for 87% of patients.

In Study AI463026, entecavir was superior to lamivudine on the coprimary endpoints of Histologic Improvement (using the Knodell Score at Week 48) and Composite Endpoint (proportion of patients with HBV DNA < 0.7 MEq/mL by bDNA assay and ALT < 1.25 X ULN at Week 48). These results and change in Ishak Fibrosis Score are shown in Table 11. Table 12 shows biochemical, virologic, and serologic endpoints.

Table 11. Histologic improvement, change in ishak fibrosis score, and composite endpoint at Week 48, lamivudine-refractory patients in Study AI463026[a]

	Entecavir 1 mg	**Lamivudine 100 mg**	**Difference Entecavir-lamivudine (97.5% CI)**
	n=124[a]	**n=116[a]**	
Histologic Improvement (Knodell Scores)			
Improvement[b]	55%	28%	27.3%[c,d] (13.6%, 40.9%)
No improvement	34%	57%	
Ishak Fibrosis Score[e]			
Improvement[e]	34%	16%	17.5%[c,f] (6.8%, 28.2%)[g]
No change	44%	42%	
Worsening[e]	11%	26%	
Missing Week 48 biopsy	11%	16%	
Composite Endpoint[h]	**n=141**	**n=145**	
	55%	4%	50.5%[d] (40.4%, 60.6%)

[a] Patients with evaluable baseline histology (baseline Knodell Necroinflammatory Score ≥ 2).
[b] ≥ 2-point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.
[c] In this analysis, missing or inadequate biopsies at Week 48 were classified "no improvement."
[d] p<0.0001.
[e] For Ishak Fibrosis Score, improvement = ≥ 1-point decrease from baseline and worsening = ≥ 1-point increase from baseline.
[f] p<0.01.
[g] 95% confidence interval.
[h] Composite Endpoint (a coprimary endpoint) was defined as HBV DNA < 0.7 MEq/mL by bDNA assay and normalisation of serum ALT (< 1.25 X ULN) at Week 48.
CI = confidence interval

Table 12. Biochemical, virologic, and serologic endpoint at Week 48, lamivudine-refractory patients in Study AI463026

	Entecavir 1 mg N=141	Lamivudine 100 mg n=145	Difference Entecavir-lamivudine (95% CI)
ALT normalisation (≤1 x ULN)	61%	15%	45.8% [a] (35.9%, 55.8%)
HBV DNA Mean change from baseline by PCR[b] (log_{10} copies/mL)	-5.11	-0.48	-4.39[a] (-4.8, -4.0)
Proportion undetectable (<300 copies/mL) by PCR[b,c]	19%	1%	17.8%[a] (11.0%, 24.5%)
<0.7 MEq/mL by bDNA[d]	66%	6%	60.4% [a] (51.8%, 69.1%)
Loss of HBeAg	10%	3%	
HBeAg seroconversion	8%	3%	

[a] p<0.0001.
[b] Roche COBAS Amplicor PCR assay.
[c] At Week 24, HBV DNA < 300 copies/mL by PCR was observed in 7% of entecavir-treated patients and no lamivudine-treated patients (p=0.0011) in Study AI463026 and 12% of entecavir-treated patients and 2% or lamivudine-treated patients (p=0.0749) in Study AI463014.
[d] Quantiplex bDNA assay.
CI = confidence interval.

In Study AI463026, responses for patients with baseline Knodell Fibrosis Scores of 4 (cirrhosis) were comparable to overall responses on all efficacy outcome measures (all patients had compensated liver disease). Histologic Improvement was independent of baseline HBV DNA or ALT levels.

For a subset of patients with paired liver samples in Study AI463026, the mean change from baseline in hepatic cccDNA at Week 48 was -0.6 log_{10} copies/HGEq (approximately 4-fold reduction) for entecavir-treated patients (n=74) and 0.0 log_{10} copies/HGEq for lamivudine-treated patients (n=59).

Health-related quality of life (HRQoL) was assessed in Study AI463026 using the standardised and validated EQ-5D instrument developed by the EurolQol group. After 48 weeks of therapy, entecavir-treated patients experienced significantly less worsening compared to lamivudine-treated patients in the dimensions of mobility, self care, and pain/discomfort.

Outcomes beyond 48 Weeks

Cumulative confirmed outcomes through 96 weeks for all treated lamivudine-refractory patients (n=141) demonstrate that continued treatment with entecavir resulted in an increase in the proportion of patients with HBV DNA < 300 copies/mL by PCR (30%) and ALT normalisation (≤ 1 times ULN) (85%). Through the last observation on or off treatment, 17% of entecavir-treated patients had HBeAg seroconversion. The difference between the entecavir and lamivudine treatment groups was statistically significant on all three parameters (p<0.01).

For the 77 patients who continued entecavir treatment beyond 52 weeks (median 96 weeks), 40% of patients had HBV DNA < 300 copies/mL by PCR and 81% had ALT normalisation (≤ 1 times ULN) at end of dosing.

Post treatment follow-up

For the 31% of nucleoside-naive, HBeAg-positive entecavir-treated patients who met response criteria (virologic suppression by bDNA assay and loss of HBeAg) and discontinued therapy, response was sustained in 75% throughout the 24-week post-treatment follow-up period. For the 88% of nucleoside-naive, HBeAg-negative entecavir-treated patients who met response criteria (virologic suppression by bDNA assay and ALT < 1.25 X ULN), response was sustained in 46% throughout the 24-week post-treatment follow-up period. Of the 22 (16%) lamivudine-refractory patients who met response criteria (virologic response on bDNA assay and loss of HBeAg) while receiving entecavir, response was sustained in 11 (50%) throughout the 24-week post-treatment follow-up period.

Outcomes of Long-term Follow-up Study

Study AI463080 was a randomized, global, observational, open-label Phase 4 study to assess long-term risks and benefits of entecavir (0.5 mg/day or 1 mg/day) treatment as compared to other standard of care hepatitis B virus nucleos(t)ide analogues (nucs) in subjects with chronic HBV (CHB) infection.

A total of 12,485 patients with CHB were randomized (1:1), of whom 12,378 were treated to receive ETV (n=6,216) or other standard of care HBV nucleoside (acid) treatment (non-ETV) (n=6,162) respectively. The patients were evaluated at baseline and subsequently twice a year (every 6 months) on clinical outcome events (COEs) for up to 10 years during the study. The principal COEs assessed in the study were overall malignant neoplasms, liver-related HBV disease progression, non-HCC malignant neoplasms, HCC, non-HCC HBV disease progression, and deaths, including liver-related deaths. The study data showed that ETV was not significantly associated with an increased risk of malignant neoplasms compared to use of other standard of care HBV nucs, as assessed by either the composite endpoint of overall malignant neoplasms or the individual endpoint of non-HCC malignant neoplasm. The most commonly reported malignancy was HCC followed by gastrointestinal malignancies with colorectal and gastric cancers representing the majority of the observed tumour types within the gastrointestinal system in both ETV and non-ETV groups. The data also showed that long-term ETV use was not associated with a lower occurrence of HBV disease progression or a lower rate of death overall. ETV treatment was generally well tolerated, with the reported events consistent with the cumulative safety experience. There was a greater number of treatment-related serious adverse events (SAEs) in the non-ETV vs ETV-treated subjects (0.8% vs 0.2%), primarily driven by neuropathic and musculoskeletal events occurring in subjects treated with the L-nucleosides (eg, lamivudine, telbivudine, and clevudine). The principal COE assessment is shown in Table 13:

Table 13. Principal analyses or time to adjudicated events – Randomised treated subjects

Endpoint[a]	Number of Subjects with Events		Hazard Ratio [ETV:Non-ETV]	P-value[c]
	ETV N=6,216	Non-ETV N=6,162		
Primary endpoints				
Overall malignant neoplasm	331	337	0.93 (0.800, 1.084)	0.3553
Liver-related HBV disease progression	350	375	0.89 (0.769, 1.030)	0.1182
Death	238	264	0.85 (0.713, 1.012)	0.0676
Secondary endpoints				
Non-HCC malignant neoplasm	95	81	1.10 (0.817, 1.478)	
HCC	240[d]	263	0.87 (0.727, 1.032)	
Liver-related death	46	48	0.91 (0.608, 1.365)	
Post-hoc exploratory endpoint				
Non-HCC HBV disease progression	137	146	0.90 (0.712, 1.135)	

[a] Overall malignant neoplasm is a composite event of HCC or non-HCC malignant neoplasm. Liver-related HBV disease progression is a composite event of liver-related death, HCC, or non-HCC HBV disease progression.[b] 95.03% CI for overall malignant neoplasm, death, and liver-related HBV disease progression; 95% CI for non- HCC malignant neoplasm, HCC, liver-related death, and non-HCC HBV disease progression.

[c] P-values are provided to the COEs that are primary endpoints per protocol specification.

[d] One subject had a pre-treatment HCC event and was excluded from the analysis.

CI = confidence interval; N = total number of subjects.

Special populations

Patients with decompensated liver disease

Study AI463048 was a randomised, open-label study of entecavir versus adefovir dipivoxil in 191 (of 195 randomised) patients with HBeAg-positive or -negative chronic HBV infection and evidence of hepatic decompensation, defined as Child-Turcotte-Pugh (CTP) score of 7 or higher. Patients were either HBV-treatment naïve or pretreated (excluding pretreatment with entecavir, adefovir dipivoxil, or tenofovir disoproxil fumarate). At baseline, patients had a mean serum HBV DNA by PCR of 7.83 $\log_{10}$ copies/mL and mean ALT level of 100 U/L; 54% of patients were HBeAg-positive; 35% had genotypic evidence of lamivudine resistance. The baseline mean CTP score was 8.6. The dose of entecavir in this study was 1 mg once daily. Entecavir was superior to adefovir dipivoxil on the primary efficacy endpoint of mean change from baseline in serum HBV DNA by PCR at Week 24. Results for selected study endpoints at Weeks 24 and 48 are shown in Table 14.

Table 14. Selected endpoints at Weeks 24 and 48, patients with decompensated liver disease, Study AI463048

	Week 24		Week 48	
	Entecavir 1mg (n=100)	**Adefovir Dipivoxil 10mg (n=91)**	**Entecavir 1mg (n=100)**	**Adefovir Dipivoxil 10mg (n=91)**
HBV DNA [a]				
Proportion undetectable (<300 copies/mL)	49%*	16%	57%*	20%
Mean change from baseline (log_{10} copies/mL)	-4.48*	-3.40	-4.66	-3.90
Stable or improved CTP score[b]	66%	71%	61%	67%
Model for End-Stage Liver Disease (MELD) score				
Mean change from baseline[c]	-2.0	-0.9	-2.6	-1.7
HBsAg loss	1%	0	5%	0
Normalisation of:[d]				
ALT (≤ 1 X ULN)	46/78 (59%)*	28/71 (39%)	49/78 (63%)*	33/71 (46%)
Albumin (≥ 1 X LLN)	20/82 (24%)	14/69 (20%)	32/82 (39%)	20/69 (29%)
Bilirubin (≤ 1 X ULN)	12/75 (16%)	10/65 (15%)	15/75 (20%)	18/65 (28%)
Prothrombin time (≤ 1 X ULN)	9/95 (9%)	6/82 (7%)	8/95 (8%)	7/82 (9%)

[a] Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).
[b] Defined as decrease or no change from baseline in CTP score
[c] Baseline mean MELD score was 17.1 for ETV and 15.3 for adefovir dipivoxil.
[d] Denominator is patients with abnormal values at baseline
*p<0.05
ULN = upper limit of normal, LLN = lower limit of normal

HIV/HBV co-infected patients

Study AI463038 was a randomised, double-blind, placebo-controlled study of entecavir versus placebo in 68 patients co-infected with HIV and HBV who were lamivudine refractory (experienced recurrence of HBV viraemia while receiving a lamivudine-containing HAART

[highly active antiretroviral therapy] regimen). Patients continued their lamivudine-containing HAART regimen (lamivudine dose 300 mg/day) and were assigned to add either entecavir 1 mg once daily (51 patients) or placebo (17 patients) for 24 weeks followed by an open-label phase for an additional 24 weeks where all patients received entecavir. At baseline, patients had a mean serum HBV DNA level by PCR of 9.13 log_{10} copies/mL. Most patients were HBeAg-positive at baseline, with a mean baseline ALT level of 71.5 U/L. Biochemical and virologic endpoints at Week 24 are shown in Table 15.

Table 15. Biochemical and virologic endpoints at Week 24, Study AI463038

	Entecavir 1mg[a] n=51	**Placebo[a] N=17**	**Difference Entecavir-Placebo (95% CI)**
HBV DNA (by PCR assay [b])			
Proportion undetectable (≤ 300 copies/mL)	6%	0	5.9% (-0.6, 12.3)
Mean change from baseline (log_{10} copies/mL)	-3.65	+0.11	-3.75[c] (-4.47, -3.04)
ALT normalisation (≤ 1xULN)[d]	34%	8%	26.0[d] (3.8, 48.1)

[a] All patients also received a lamivudine-containing HAART regimen.
[b] Roche COBAS Amplicor PCR assay
[c] p<0.0001
[d] n=35 for entecavir and n=12 for placebo
[e] p = 0.08

At the end of the open-label phase (Week 48), the mean change from baseline HBV DNA by PCR for patients originally assigned to entecavir monohydrate was -4.20 log_{10} copies/mL; 8% of patients had HBV DNA < 300 copies/mL by PCR; and 37% patients with abnormal ALT at baseline had ALT normalisation (≤ 1 times ULN). Entecavir has not been evaluated in HIV/HBV co-infected patients who are not concurrently receiving effective HIV treatment (see Section 4.4 Special warnings and precautions for use – Co-infection with HIV).

Liver transplant recipients

The safety and efficacy of entecavir 1 mg once daily were assessed in a single-arm, open label study in 65 patients who received a liver transplant for complications of chronic HBV infection and had HBV DNA < 172 IU/mL (approximately 1000 copies/mL) at the time of transplant. The study population was 82% male, 39% Caucasian, and 37% Asian, with a mean age of 49 years; 89% of patients had HBeAg-negative disease at the time of transplant. Of the 61 patients who were evaluable for efficacy (received entecavir for at least 1 month), 60 also received hepatitis B immune globulin as part of the post-transplant prophylaxis regimen. At Week 72 post-transplant, none of the evaluable patients had HBV recurrence [defined as HBV DNA ≥ 50 IU/mL (approximately 300 copies/mL)] by last-observation-carried forward analysis.

The frequency and nature of adverse events in this study were consistent with those expected in patients who have received a liver transplant and the known safety profile of entecavir.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

In healthy participants, entecavir monohydrate was rapidly absorbed with peak plasma concentrations occurring between 0.5 and 1.5 hours. There was a dose-proportionate increase in peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) values following multiple doses ranging from 0.1 to 1 mg. Steady-state was achieved after 6-10 days of once-daily dosing with approximately 2-fold accumulation. C_{max} and trough plasma concentration (C_{trough}) at steady-state were 4.2 and 0.3 ng/mL, respectively, for a 0.5 mg dose, and 8.2 and 0.5 ng/mL, respectively, for a 1 mg dose. In healthy participants, the bioavailability of the tablet was 100% relative to the oral solution. The oral solution and tablet may be used interchangeably.

Oral administration of entecavir monohydrate 0.5 mg 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 minimal delay in absorption (1-1.5 hour fed vs. 0.75 hour 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 before a meal and at least 2 hours after a meal) (see Section 4.2 Dose and method of administration).

Distribution

The estimated volume of distribution for entecavir monohydrate was in excess of total body water, suggesting that it has good penetration into tissues. Protein binding to human serum protein *in vitro* was approximately 13%.

Metabolism

Entecavir monohydrate is not a substrate, inhibitor, or inducer of the CYP450 enzyme system. At concentrations approximately 10,000-fold higher than those obtained in humans, entecavir monohydrate inhibited none of the major human CYP450 enzymes 1A2, 2C9, 2C19, 2D6, 3A4, 2B6, and 2E1. At concentrations approximately 340-fold higher than those observed in humans, entecavir monohydrate did not induce the human CYP450 enzymes 1A2, 2C9, 2C19, 3A4, 3A5, and 2B6. Following administration of ^{14}C-entecavir monohydrate in humans and rats, no oxidative or acetylated metabolites and minor amounts of the phase II metabolites glucuronide and sulfate conjugates were observed.

Excretion

After reaching peak levels, entecavir monohydrate 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 about 24 hours.

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

Special Populations

Gender/race

The pharmacokinetic profile of entecavir monohydrate does not vary by gender or race.

Elderly

The pharmacokinetic profile of entecavir monohydrate does not vary by age.

Renal impairment

The pharmacokinetics of entecavir monohydrate following a single 1 mg dose were studied in patients (without chronic hepatitis B infection) with selected degrees of renal impairment, including patients whose renal impairment was managed by haemodialysis or CAPD. Results are shown in Table 16.

Table 16. Pharmacokinetic parameters of entecavir monohydrate in participants with selected degrees of renal impairment

	Renal Function Group Baseline Creatinine Clearance (mL/min)					
	Unimpaired > 80 (n=6)	**Mild > 50- ≤ 80 (n=6)**	**Moderate 30-50 (n=6)**	**Severe < 30 (n=6)**	**Severe Managed with Haemodialysis (n=6)**	**Severe Managed with CAPD (n=4)**
C_{max} (ng/mL) (CV%)	8.1 (30.7)	10.4 (37.2)	10.5 (22.7)	15.3 (33.8)	15.4 (56.4)	16.6 (29.7)
AUC ($_{0-T}$) (ng•hr/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)

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

Dosage adjustment is recommended for patients with a creatinine clearance < 50 mL/min, including patients on haemodialysis or CAPD. (See Section 4.2 Dose and method of administration – Renal Impairment).

Following a single 1 mg dose of entecavir monohydrate, haemodialysis removed approximately 13% of the entecavir monohydrate dose over 4 hours and CAPD removed approximately 0.3% of the dose over 7 days. Entecavir monohydrate should be administered after haemodialysis.

Hepatic impairment

The pharmacokinetics of entecavir monohydrate following a single 1 mg dose were studied in patients (without chronic hepatitis B infection) with moderate and severe hepatic impairment. The pharmacokinetics of entecavir monohydrate were similar between hepatically impaired patients and healthy control participants; therefore, no dosage adjustment of entecavir is recommended for patients with hepatic impairment.

Post-liver transplant

Entecavir monohydrate exposure in HBV-infected liver transplant recipients on a stable dose of cyclosporine A (n=5) or tacrolimus (n=4) was approximately 2-fold the exposure in healthy participants with normal renal function. Altered renal function contributed to the increase in

entecavir monohydrate exposure in these patients. Before and during entecavir therapy in liver transplant recipients receiving cyclosporine or tacrolimus, renal function should be carefully evaluated (see Section 4.2 Dose and method of administration – Renal Impairment).

Paediatric use

Pharmacokinetic studies have not been conducted in children.

Drug interactions (see Section 4.5 Interactions with other medicines and other forms of interactions)

Entecavir monohydrate is not a substrate, inhibitor, or inducer of the CYP450 enzyme system (see Section 5.2 Pharmacokinetic properties – Metabolism). The pharmacokinetics of entecavir monohydrate are unlikely to be affected by coadministration with agents that are either metabolised by, inhibit, or induce the CYP450 system. Likewise, the pharmacokinetics of known CYP substrates are unlikely to be affected by coadministration of entecavir monohydrate.

The steady-state pharmocokinetics of entecavir monohydrate and coadministered drug were not altered in interaction studies of entecavir monohydrate with each of the following:

- lamivudine,
- adefovir dipivoxil,
- tenofovir disoproxil fumarate (see also Section 4.5 Interactions with other medicines and other forms of interactions**)**.

A pilot study in nine HBV-infected liver transplant recipients suggested that concurrent ciclosporine A (n=5) or tacrolimus (n=4) therapy did not affect the pharmacokinetics of entecavir monohydrate (see Section 5.2 Pharmacokinetic properties – Special Populations, Post-liver transplant). The effect of entecavir monohydrate on the pharmacokinetics of cyclosporine A or tacrolimus is unknown.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

No evidence of genotoxicity was observed in an Ames microbial mutagenicity assay, a mammalian-cell gene mutation assay, and a transformation assay with Syrian hamster embryo cells. Results of an oral micronucleus study and an oral DNA repair study in rats were also negative. Entecavir was clastogenic to human lymphocyte cultures at ≥ 2350 times the Cmax in humans at 0.5 mg/day (approximately 1200 times at 1 mg/day).

Carcinogenicity

Two year carcinogenicity studies with entecavir monohydrate were conducted in mice and rats. In male mice, increases in the incidences of lung tumours were observed at exposures ≥ 5 times that in humans at 0.5 mg/day (≥ 3 x at 1 mg/day). Tumour development was preceded by pneumocyte proliferation in the lung, which was not observed in rats, dogs, or monkeys, supporting the conclusion that lung tumours observed in mice are species-specific events not relevant to humans. Increased incidences of other tumours were seen only at the highest exposures [in mice approximately 70 times human exposure at 0.5 mg/day (approximately 40 times at 1 mg/day) and in rats 62 times (males) and 43 times (females) human exposure at 0.5 mg/day (35 and 24 times, respectively, at 1 mg/day)], including liver carcinomas in male mice,

benign vascular tumours in female mice, brain gliomas in male and female rats, and liver adenomas and carcinomas in female rats. These tumour findings are unlikely to be relevant to humans.

Impairment on fertility

In toxicology studies in rodents and dogs, seminiferous tubular degeneration was observed at ≥ 62 and ≥ 35 times human exposure at 0.5 and 1 mg/day, respectively. No testicular changes were evident in a 1-year study in monkeys at exposures 296 times human exposure at 0.5 mg/day (167 times at 1 mg/day). There were no effects on fertility in male rats at exposures > 160 times human exposure at 0.5 mg/day (> 90 times at 1 mg/day). In female rats, no effects on fertility or early embryonic development were observed at exposures > 165 times human exposure at 0.5 mg/day (> 94 times at 1 mg/day).

Reproductive studies

When entecavir was orally administered to presumed-pregnant rats, no drug-related changes were observed in either dams or fetuses at maternal exposures approximately 50 times human exposure at 0.5 mg/day (28 times at 1 mg/day). At maternal exposures ≥ 318 human exposure at 0.5 mg/day (≥ 180 times at 1 mg/day), embryo-fetal toxicity (resorptions) and maternal toxicity were observed, and at exposure 5498 times human exposure at 0.5 mg/day (3100 times at 1 mg/day), lower fetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternebrae, and phalanges), and extra lumbar vertebrae and ribs were observed. When entecavir was orally administered to presumed-pregnant rabbits, no drug-related developmental changes were noted at systemic exposures up to 377 times that in humans at 0.5 mg/day (212 times at 1 mg/day). At exposure 1566 times human exposure at 0.5 mg/day (883 times at 1 mg/day), embryo-fetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed. In an oral study of prenatal and postnatal development in rats, entecavir did not affect offspring at exposures >165 times human exposure at 0.5 mg/day (> 94 times at 1 mg/day).

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Entecavir Sandoz 0.5 mg and 1 mg film-coated tablets contain lactose monohydrate, microcrystalline cellulose, crospovidone, hypromellose, magnesium stearate, macrogol 6000, titanium dioxide and purified talc. The 1 mg tablet coating contains iron oxide red and iron oxide yellow.

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF LIFE

Blister packs: 36 months.

Bottles: 24 months.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5. NATURE AND CONTENTS OF CONTAINER

0.5 mg: blister packs (Alu/Alu) and bottles* (HDPE) of 30 tablets.

1 mg: blister packs (Alu/Alu) and bottles* (HDPE) of 30 tablets.

*Presentation not marketed

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

17/05/2018

10. DATE OF REVISION OF THE TEXT

20/03/2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Change in sponsor details