New Zealand Datasheet

1 PRODUCT NAME

Entecavir 0.5 mg film coated tablet
Entecavir 1 mg film coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Entecavir 0.5 mg and 1 mg (as monohydrate) tablets.

Excipient(s) with known effect:
Each 0.5 mg film-coated tablet contains 119.468 mg of lactose.
Each 1 mg film-coated tablet contains 238.936 mg of lactose.

For the full list of excipients, refer to Section 6.1.

3 PHARMACEUTICAL FORM

0.5 mg film-coated tablet: White to off-white, triangular shaped, biconvex, film-coated tablet, debossed with 'E' on one side and plain on other side.

1 mg film-coated tablet: Pink coloured, triangular shaped, biconvex, film-coated tablet, debossed with "E" on one side and "1" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Entecavir tablets are indicated for the treatment of chronic Hepatitis B Virus (HBV) infection in adults with evidence of active liver inflammation.

4.2 Dose and method of administration

Recommended Dosage
Entecavir tablets are to be taken on an empty stomach (at least two hours before a meal and at least two hours after a meal).

The recommended oral dose is 0.5 mg once per day in adults (older than 16 years). The recommended oral dose is 1 mg once per day for lamivudine-refractory patients [evidence of viremia while treated with lamivudine or the occurrence of LVDR (YMDD) mutations].

Renal Impairment
In individuals with renal impairment, the evident entecavir oral clearance reduced as creatinine clearance decreased (Refer to Section 5.1 - Pharmacodynamic Properties - Special Populations). For patients with a creatinine clearance of <50 mL/min, dosage adjustment is recommended. This includes patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) or haemodialysis, as shown below in Table 1 and 2.

Recommended Tablet Dosage in Renal Impairment:

Table 1: Schedule-Based Method Recommended for Entecavir Tablets Dosage in Patients with Renal Impairment

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

*On days of haemodialysis - administer following haemodialysis.

Table 2: Dose Reduction Method Recommended for Entecavir Tablets Dosage in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Usual Dose (0.5 mg)	Lamivudine Refractory (1 mg)
≥50 mL/min	0.5 mg once per day	1 mg once per day
30 to <50 mL/min	0.25 mg once per day§	0.5 mg once per day
10 to <30 mL/min	0.15 mg once per day§	0.3 mg once per day§
<10 mL/min	0.05 mg once per day§	0.1 mg once per day§
Haemodialysis or CAPD*	0.05 mg once per day	0.1 mg once per day

§ For doses <0.5 mg please enquire about alternative treatments. **Do not split tablets.**
*On days of haemodialysis - administer following hemodialysis.

Hepatic Impairment
No adjustment of dose is required for patients with hepatic impairment.

Therapy Duration
The optimal duration of entecavir treatment for individuals with chronic hepatitis B infection and the association between therapy and long-term outcomes such as hepatocellular carcinoma and cirrhosis is not known.

4.3 Contraindications

Entecavir tablets are contraindicated in individuals with previous hypersensitivity to entecavir or any other excipient of the product (refer to section 6.1 Excipients).

4.4 Special warnings and precautions for use

Lactic acidosis
There have been reports of lactic acidosis and severe hepatomegaly with steatosis, (involving fatal cases), with the administration of nucleoside analogues only, or concomitantly with antiretrovirals.

Hepatitis exacerbations following treatment discontinuation
In patients that have withdrawn from hepatitis B treatment (including entecavir therapy), acute exacerbation of hepatitis has been reported (refer to Section 4.8 Undesirable Effects). Most of the post-treatment exacerbations appear to be self-limited. However, serious exacerbations including fatal cases may occur. The contributing relationship of these occurrences to treatment discontinuation is not known. Following discontinuation, hepatic

function should be monitored at recurring intervals. If suitable, recommencement of hepatitis B therapy may be justified.

Renal Impairment
It is recommended for patients with renal impairment to have their entecavir dosage adjusted (refer to Section 5.2 **–** Pharmacokinetic Properties - Renal impairment).

Liver Transplant Patients
Before and throughout entecavir treatment renal function must be carefully monitored in liver transplant patients when receiving cyclosporine or tacrolimus (refer to Section 4.2 – Undesirable Effects - hepatic impairment, and Section 5.2 – Pharmacodynamic Properties - hepatic impairment, and post liver transplant).

Decompensated Liver Disease
Refer to Section 5.1 Pharmacodynamic Properties - Clinical trials and 4.8 Undesirable effects for information on a study of entecavir 1 mg/day that has been undertaken in patients with decompensated liver disease.

Co-infection with Hepatitis C or D
There is no information on the effectiveness of entecavir in patients co-infected with hepatitis C or D.

Lactose
This product contains 119.468 mg of lactose in each 0.5 mg tablet and 238.936 mg of lactose in each 1 mg tablet. Caution should be taken with the use of entecavir tablets in patients with lactose intolerance.

Patients should not take entecavir tablets if they have rare hereditary problems of galactose intolerance or the Lapp lactase deficiency of glucose-galactose malabsorption.

Co-infection with HIV
Entecavir has not been studied in HIV/HBV co-infected patients not concurrently receiving HIV therapy. Entecavir treatment is not recommended in HIV/HBV co-infected patients not receiving highly active antiretroviral therapy (HAART). Limited clinical knowledge implies there is potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors in the event that entecavir is administered for the treatment of chronic hepatitis B virus infection in individuals with HIV infection that is not currently being treated.

Patient Information
While taking entecavir, patients must remain under their physicians care. Any new symptoms or other medications should be discussed with their physician.

Entecavir can be taken on an empty stomach (at least two hours before a meal and two hours after a meal).

If entecavir treatment is discontinued, patients should be advised that liver disease deterioration may result in some cases, and any changes in their treatment should be discussed with their physician.

Entecavir treatment has not been shown to decrease the risk of HBV transmission to others through blood contamination or sexual contact (refer to Section 4.6 – Fertility, Pregnancy and Lactation).

Paediatric Use
The safety and effectiveness of entecavir has not been established in paediatric patients (younger than 16 years).

Geriatric Use
There is not enough information from clinical research to determine whether patients aged 65 years and over respond differently to entecavir than younger patients. Other clinical experience reports have not acknowledged differences in reactions between the elderly and younger subjects.

In patients with reduced renal function, there is a greater risk of toxic reactions as entecavir is extensively excreted by the kidney. Because older patients are more likely to have reduced renal function, significant care must be taken when selecting the dose, and it could be helpful to monitor renal function throughout treatment (refer to Section 4.2 - Dose and Method of Administration - Renal Impairment).

4.5 Interaction with other medicines and other forms of interaction

As entecavir is mainly eliminated by the kidney (refer to Section 5.2 – Pharmacokinetic Properties - Excretion), co-administration with medications that compete for active tubular secretion or decrease renal function may increase serum concentrations of one or both medications. Co-administration of entecavir with adefovir dipivoxil, lamivudine, or tenofovir disoproxil fumarate caused no significant drug interactions. Concomitant use of entecavir with other medications that are renally excreted or may affect renal function have not been assessed, therefore, individuals must be carefully monitored for adverse events when entecavir is co-administered with other medicinal products.

The administration of entecavir with food reduces absorption. (Refer to Section 4.2 Dose and Method of Administration and Section 5.2 – Pharmacokinetic Properties - Absorption).

4.6 Fertility, pregnancy and lactation

Use in Pregnancy- Pregnancy Category B3
No acceptable controlled studies have been completed in pregnant women. Entecavir tablets must only be used in pregnancy if the potential benefit warrants the possible risk to the foetus.

There is no accessible data available on the result of entecavir on the transmission of the hepatitis B virus from mother to baby. Consequently, suitable interventions must be utilised for the prevention of neonatal acquisition of the hepatitis B virus.

In rats presumed pregnant, orally administered entecavir resulted in no observations of drug-related changes in either rats or foetuses at entecavir an exposure (28 times at 1 mg/day) of approximately 50 times human exposure at 0.5 mg/day. At maternal exposures of ≥180 times at 1 mg/day (≥318 human exposure at 0.5 mg/day), maternal toxicity and embryo-foetal toxicity (resorptions) were observed. At exposures of 3100 times at 1 mg/day (5498 times human exposure at 0.5 mg/day), observations of lower foetal body weights, extra lumbar vertebrae and ribs, vertebral and tail malformations, decreased ossification (vertebrae, phalanges and sternebrae) were reported. In rats presumed pregnant, orally administered entecavir resulted in no drug-related developmental changes at systemic exposures of 212 times at 1 mg/day (up to 377 times that in humans at 0.5 mg/day). At 883 times at 1 mg/day (exposure of 1566 times human exposure at 0.5 mg/day), observations of decreased ossification (hyoid), embryo-foetal toxicity (resorptions), and an increased

occurrence of a 13th rib were reported. In an oral clinical study on rats, entecavir did not influence the prenatal and postnatal development at exposures of >94 times at 1 mg/day (>165 times human exposure at 0.5 mg/day).

Pregnancy Registry: A Pregnancy Registry has been created to monitor pregnant women and the maternal-foetal outcomes with the use of entecavir. It is recommended that Physicians register patients by phoning 0800 167 567.

Labour and Delivery
There is no research on the labour and delivery in pregnant women and no studies on entecavir's effectiveness in the transmission of the hepatitis B virus from mother to baby. Consequently, suitable interventions must be utilised for the prevention of neonatal acquisition of the hepatitis B virus.

Lactation
Entecavir is excreted into the milk of rats. It is unknown whether entecavir is excreted into human milk. Women must be directed to not breast-feed if they are using entecavir.

4.7 Effects on ability to drive and use machines

There are no studies on the effects of entecavir on the ability to drive and the use of machinery. Some common adverse reactions reported with entecavir treatment may affect the ability to drive or operate machinery, such as fatigue, dizziness, and somnolence.

4.8 Undesirable effects

The review of adverse reactions is centred on 1720 patients with chronic hepatitis B virus infection studied over four clinical studies. Each patient was given entecavir tablets double-blind treatment of either 0.5 mg per day, entecavir 1 mg per day or lamivudine (n=679, n=183, n=858, respectively) for up to 107 weeks. The entecavir and lamivudine safety profiles were similar in these clinical studies. The most prevalent adverse reactions amongst patients treated with entecavir of any severity were headache (9%), fatigue (6%), dizziness (4%) and nausea (3%), due possibly from the usage of entecavir.

In this research, adverse reactions in patients who received blinded entecavir therapy (n=594) for more than 52 weeks were comparable in both type and severity to those described during the initial 52 weeks of therapy.

Clinical Trial Adverse Events
Clinical adverse reactions of moderate to severe intensity and considered to be possibly associated with entecavir treatment in the four clinical studies where the comparisons of entecavir and lamivudine were studied and presented in Table 3.

Table 3: Clinical Adverse Reactions[a] of Moderate to Severe Intensity (Grades 2-4) Observed in Four Entecavir Clinical Studies

	Nucleoside-Naive[b]		**Lamivudine-Refractory[c]**	
Body System/ Adverse Reaction	**Entecavir 0.5 mg (n=679)**	**Lamivudine 100 mg (n=668)**	**Entecavir 1 mg (n=183)**	**Lamivudine 100 mg (n=190)**

Gastrointestinal				
Diarrhoea (%)	<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	0
Somnolence (%)	<1	<1	0	0
Psychiatric				
Insomnia (%)	<1	<1	0	<1

[a] Includes reactions of possible, probable, certain or unknown relationship to treatment regimen.
[b] Phase 3 Studies AI463022 (Study A) and AI463027 (Study B).
[c] Includes Phase 3 Study AI463026 (Study C) and the treatment arms of entecavir 1 mg and lamivudine of the Phase 2 Study AI463014 (Study D), a multinational, double-blind, randomized study of three entecavir doses (0.1 mg, 0.5 mg, and 1 mg) once per day versus continued lamivudine 100 mg once per day for up to 52 weeks in individuals who experienced recurring viremia on lamivudine treatment.

Laboratory Findings
Table 4 presents the laboratory results from four lamivudine-controlled, double-blind, clinical trials in which nucleoside-naive patients were given entecavir 0.5 mg once per day (n=679) for a median of 53 weeks and lamivudine-refractory patients were given entecavir 1 mg (n=183) for a median of 69 weeks.

Table 4: Laboratory Abnormalities Observed During Four Clinical Trials Treatment

Test	**Nucleoside-Naive[a] Entecavir 0.5 mg** n=679	**Lamivudine-Refractory[b] Entecavir 1 mg** 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 = 53 weeks
[b] Median duration of therapy = 69 weeks
ULN = Upper Limit of Normal

Between patients treated with entecavir, with sustained treatment, on-treatment ALT

elevations >10 X ULN and >2 X baseline usually resolved. Most of these exacerbations were connected with a >2 log10/mL decrease in viral load that preceded or overlapped with the elevation of ALT. It is recommended throughout treatment, the hepatic function is periodically monitored.

Exacerbations of Hepatitis Following Treatment Discontinuation
There are reports of hepatitis acute exacerbations in patients who have withdrawn from anti-HBV treatment, including entecavir therapy. The hepatitis exacerbation frequency (or ALT flare - defined as ALT >10X ULN and 2X the patient's reference level) in clinical trials with entecavir throughout off-treatment follow-up is shown in Table 5.

Table 5: Exacerbation of Hepatitis in Three Clinical Studies During Off-Treatment Follow-up

	Patients with ALT Elevations >10 X ULN and > 2X Reference[a]			
	Entecavir		**Lamivudine**	
	N	%	N	%
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	0

[a] Reference = the baseline minimum or final measurement at dosing end. Median time was 23 weeks to off-treatment exacerbation for patients treated with entecavir and 10 weeks for patients treated with lamivudine.

Patients with Decompensated Liver Disease
Clinical adverse reactions reported in Study F through Week 48 in which entecavir 1 mg once per day was evaluated against adefovir dipivoxil in individuals with chronic hepatitis B infection and decompensated liver disease is shown in Table 6. The cumulative rates for the discontinuation for adverse events and on-study of death and hepatocellular carcinoma (HCC) are also reported.

Table 6: Safety Outcomes in Study F (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		
Gastrointestinal Disorders		
Vomiting (%)	<1	1
Diarrhoea (%)	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 Conditions		
Fatigue (%)	<1	1

Discontinuation for Adverse Event (cumulative) (%)	7	6
Deaths (cumulative) (%) **Hepatocellular Carcinoma (cumulative) (%)**	23 12	33 20

[a] Contains adverse events of possible, probable, certain or unknown relationship to the therapy schedule.

Causes of death were usually liver-related, as anticipated in this population. The onset time of HCC or death (whichever happened first) was similar between the two treatment groups.

Laboratory test abnormalities observed in Study F through week 48 are reported in Table 7.

Table 7: Laboratory Abnormalities in Study Observed Through Week 48

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 infected with both HBV and Human Immunodeficiency Virus (HIV) who experienced HBV viremia recurrence when being treated with a lamivudine-containing highly active antiretroviral were administered a lamivudine-containing treatment (lamivudine dose, 300 mg per day) and either entecavir 1 mg once per day or placebo. Following 24 weeks of double-blind treatment and a mean of 17 weeks of open label treatment (where all patients were given entecavir), the adverse reactions and laboratory abnormality profiles were comparable for the entecavir and placebo treatment groups. Entecavir has not been studied in co-infected HIV/HBV patients who are not simultaneously receiving HIV treatment (refer to Section 4.4 – Special Warnings and Precautions of Use - Co-infection with HIV).

Post-Marketing Experience
The subsequent adverse events have been recorded during post-approval entecavir use. An estimation of frequency is unable to be made as the reports are voluntary from an unknown population size.

Hepatobiliary disorders: Transaminases increased
Immune system disorders: Anaphylactoid reaction
Metabolism and nutrition disorders: There have been reports of lactic acidosis, frequently associated with hepatic decompensation, further serious medical conditions, or drug exposures. Individuals with decompensated cirrhosis might be at

	an increased risk for lactic acidosis.
Skin and subcutaneous tissue disorders:	Alopecia and rash

Reporting of suspected adverse reactions

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 minimal knowledge of patient entecavir overdose. No unexpected adverse events or an increase in adverse events were observed in healthy individuals who were given a single dose of entecavir (up to 40 mg), or several doses (up to 20 mg per day for up to 14 days). In the event of overdose, the patient should be carefully monitored for toxicity, and typical supportive treatment given, if required.

A 4-hour session of haemodialysis following an individual dose of 1 mg entecavir, eliminated approximately 13% of entecavir administered.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacological Actions

Mechanism of Action

Entecavir is a guanosine nucleoside analogue and has effective and selective activity against HBV polymerase. Entecavir is phosphorylated to active triphosphate (TP), with an intracellular 15-hour half-life. The levels of intracellular TP are completely related to the concentration of extracellular entecavir, with no significant build-up outside of the initial plateau levels. By contending with the natural substrate deoxyguanosine TP, entecavir-TP inhibits the function of all three viral polymerase activities: One - HBV polymerase priming, two - reverse transcription of the pregenomic messenger RNA negative strand, and three - the synthesis of the positive strand HBV DNA. The HBV DNA polymerase entecavir-TP Ki is 0.0012 µM. For the cellular DNA polymerases α, β, and δ with Ki values of 18 to 40 µMm entecavir-TP is a weak inhibitor. Furthermore, elevated exposures of entecavir had no significant adverse effects on mitochondrial DNA synthesis in HepG2 cells (Ki >160 µM) or γ polymerase.

Resistance in vitro

There was decreased receptiveness to entecavir with the attendance of LVDR substitutions. Entecavir prevented LVDR HBV replication at greater concentrations (8-fold) than that for the wild-type virus in cell-based trials. The intracellular entecavir-TP would be anticipated to exceed those required at extracellular concentrations the plasma level representative attained with dosing of 1 mg, to prevent the enzyme activity of lamivudine-resistant HBV polymerases. Recombinant viruses containing adefovir-resistant replacements at either

rtN236T or rtA181V continued to be fully susceptible to entecavir.
Strains that were lamivudine-resistant containing rtL180M plus rtM204V in combination with amino acid substitution rtA181C presented 16 to 122 fold decreases in entecavir phenotypic susceptibility.

Clinical Resistance
Patients in clinical studies originally given entecavir 0.5 mg (nucleoside-naive) or 1.0 mg (lamivudine-refractory) treatment and with a measurement of on-therapy PCR HBV DNA at week 24 or after were carefully examined for resistance. Due to resistance, virologic rebounds to entecavir need the preceding existence of primary LVDr substitutions (M204I/V ± L180M) including an extra substitution at residues T184, S202, and/or M250 of the polymerase protein.

Nucleoside-naïve studies: Evidence of entecavir resistance (ETVr) substitutions at rtT184, rtS202, or rtM250 through week 240 were identified in three subjects given entecavir treatment. Table 8 shows two patients experienced virologic breakthrough. The observation of these substitutions were only seen in the existence of LVDr substitutions (rtM204V/I±rtL 180M). The accumulative probability of developing genotypic ETVr substitutions in nucleoside-naive trials were 0.2% for Year 1, 0.5% for Year 2, 1.2% for Year 3, 1.2% and for Year 4 and 1.2% for Year 5.

Table 8: Nucleoside-Naïve Trials of Emerging Genotypic Resistance Over 5 Years

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

[a] Year 3 results show the use of entecavir 1-mg dose for 147 of 149 patients and all patients in Years 4 and 5 (121 and 108, respectively) and of combination entecavir-lamivudine treatment (followed by entecavir treatment long-term) 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 a rollover trial.
[b] Includes individuals with at least one PCR on-therapy HBV DNA measurement at Year 1 (after week 24 through week 58), Year 2 (after week 58 through week 102), Year 3 (after week 102 through week 156), Year 4 (after week 156 through week 204), or Year 5 (after week 204 through week 252.
[c] Patients have in addition LVDr substitutions.
[d] ≥ log10 increase exceeding nadir in HBV DNA by PCR, verified with consecutive measurements or at the completion of the windowed time point.

Lamivudine-refractory studies: ETVr substitutions were detected at baseline in isolates from 10 of 187 lamivudine-refractory patients (5%) treated with entecavir and observed for resistance (in addition to LVDr substitutions rtM204V/I ± rtL180M). This indicates that previous treatment of lamivudine can choose these resistance substitutions and that they can happen prior to entecavir therapy at a low frequency. Three of the ten subjects experienced virologic breakthrough (≥ log10 increase above nadir) through week 240. Table 9 shows the developing entecavir resistance in lamivudine-refractory trials through

week 240.

Table 9: Lamivudine-Refractory Trials of Emerging Genotypic Entecavir Resistance Over 5 Years

	Year 1	Year 2	Year 3[a]	Year 4[a]	Year 5[a]
Patients monitored and treated for resistance[b] (n)	187	146	80	52	33
Patients in year with:					
- emerging genotypic ETVr[c] (n)	11	12	16	6	2
- genotypic ETVr[c] with virologic breakthrough[d] (n)	2[e]	14[e]	13[e]	9[e]	1[e]
Cumulative probability of:					
-emerging genotypic ETVr[c] (%)	6	15	36	47	51
- genotypic ETVr[c] with virologic breakthrough[d] (%)	1[e]	11[e]	27[e]	41[e]	44[e]

[a] Results show the use of a combination entecavir-lamivudine treatment (followed by entecavir treatment, long-term) for a median of 13 weeks for 48 of 80 patients in Year 3, 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 a rollover trial.
[b] Includes individuals with at least one PCR on-therapy HBV DNA measurement at Year 1 (at or after week 24 through week 58), Year 2 (after week 58 through week 102), Year 3 (after week 102 through week 156), Year 4 (after week 156 through week 204, or Year 5 (after week 204 through week 252).
[c] Patients have in addition LVDr substitutions.
[d] ≥1 log10 increase exceeding nadir in HBV DNA by PCR, verified with consecutive measurements or at the completion of the windowed time point.
[e] ETVr happening in any year, virologic breakthrough in specified year.

Phase 2 and 3 Clinical Studies Integrated Analysis
In entecavir resistance data from seventeen Phase 2 and 3 clinical trials, a post-approval integrated analysis showed a developing entecavir resistance - related substitution rtA181C was identified in five of 1461 patients during entecavir treatment. This substitution was identified only in the occurrence of lamivudine resistance-associated substitutions rtL180M plus rtM204V.

Clinical Trials
The evaluation of safety and efficacy of entecavir tablets were completed in four active-controlled studies over five continents. The trials included 1720 individuals with chronic hepatitis B infection (serum HBsAg-positive for at least six months), with evidence of viral replication (measurable serum HBV DNA, as calculated by the bDNA hybridisation or PCR assay). Individuals were 16 years of age or older. Patients in the Phase 3 Studies (Study A) AI463022, (Study C) AI463026, and (Study B) AI463027 had continually increased ALT levels of ≥1.3 times the upper limit of normal (ULN) and chronic inflammation on liver biopsy similar with a chronic viral hepatitis diagnosis. In comparison to the Phase 2 Study where abnormal ALT was not an entry criterion and liver biopsy was non-compulsory. The evaluation of safety and efficacy of entecavir was also assessed in an active-controlled trial of 191 HBV-infected individuals with decompensated liver disease and in a trial of 68 patients co-infected with HIV and HBV.

Nucleoside-Naive Patients with Compensated Liver Disease

HBeAg-positive

One Phase 3 Study (Study A) AI463022 was a randomised, multinational, double-blind trial in 709 (of 715 randomised) nucleoside-naive individuals with chronic hepatitis B infection and detectable HBeAg who were treated with entecavir 0.5 mg once per day versus lamivudine 100 mg once per day over 52 weeks. The ethnic distribution was 57% Asian and 40% Caucasian, with a mean age of 35 years (range of 16 to 78), and 75% were male. Previously 13% had been given interferon-α therapy. Patients had a mean serum HBV DNA level as assessed by Roche COBAS Amplicor® PCR assay of 9.66 log10 copies/mL, a mean Knodell Necroinflammatory Score of 7.8, and a mean serum ALT level of 143 U/L at baseline. For 89% of the individuals, paired adequate liver biopsy samples were accumulated.

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

One Phase 3 Study B (AI463027) was a randomised, multinational, double-blind trial in 638 (of 648 randomised) nucleoside-naive individuals with HBeAg-negative (HBeAb-positive) chronic hepatitis B infection (assumed to have pre-core or core-promoter mutants), treated with entecavir 0.5 mg once per day versus lamivudine 100 mg once per day over 52 weeks. The ethnic distribution was 39% Asian and 58% Caucasian, with a mean age of 44 years (range of 18 to 77), and 76% were male. Previously, 13% had been given interferon-α treatment. Patients had a mean serum HBV DNA level as assessed by Roche COBAS Amplicor®PCR assay of 7.58 log10 copies/mL, a mean Knodell Necroinflammatory Score of 7.8, and a mean serum ALT level of 141.7 U/L at baseline. For 98% of the individuals a baseline liver biopsy was completed, and for 89% a biopsy was completed at week 48; paired samples were accumulated for 88% of patients. The assessed response was completed at week 52 based on test results received at the week 48 visit.

In both Phase 3 studies above: Study A (AI463022) and Study B (AI463027); entecavir was better than lamivudine on the Histologic Improvement primary efficacy endpoint, determined as ≥2-point reduction in Knodell Necroinflammatory Score with no deterioration in the Knodell Fibrosis Score at week 48. Table 10 shows the Histologic Improvement and variation in Ishak Fibrosis Scores. Biochemical, serologic and virologic outcome measures are shown in Table 11.

Table 10: Histologic Improvement and Change at Week 48 in Ishak Fibrosis Score, Nucleoside-Naive Patients in Two Phase 3 Studies: Study A (AI463022) and Study B (AI463027)

	Phase 3 Study (Study A) AI463022 (HBeAg-Positive)			**Phase 3 Study (Study B) AI463027 (HBeAg-Negative)**		
	Entecavir 0.5 mg n=314[a]	**Lamivudine 100 mg n=314[a]**	**Difference Entecavir - Lamivudine (95% CI)[b]**	**Entecavir 0.5 mg n=296[a]**	**Lamivudine 100 mg n=287[a]**	**Difference Entecavir - Lamivudine (95% CI)[b]**
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	
Deteriorating[f] (%)	8	10		12	15	
Unsatisfactory Week 48 biopsy (%)	2	5		2	1	
Missing Week 48 biopsy (%)	5	9		8	11	

[a] Individuals with evaluable baseline histology (baseline Knodell Necroinflammatory Score ≥2).
[b] Missing or unsatisfactory biopsies at week 48 were classified "no improvement."
[c] ≥2-point decrease in Knodell Necroinflammatory Score from baseline with no deteriorating of the Knodell Fibrosis Score.
[d] p<0.01
[e] p<0.05
[f] For Ishak Fibrosis Score, improvement = ≥1-point reduction from baseline and deteriorating = ≥1-point increase from baseline.
[g] Not significant.
CI = confidence interval.

Table 11: Biochemical, Serologic and Virologic Endpoints at Week 48, Nucleoside-Naive Patients in Two Phase 3 Studies (A and B)

	Phase 3 Study (Study A) (HBeAg-Positive) AI463022			**Phase 3 Study (Study B) (HBeAg-Negative) AI463027**		
	Entecavir 0.5 mg n=354	**Lamivudine 100 mg n=355**	**Difference Entecavir - Lamivudine (95% CI)**	**Entecavir 0.5 mg n=325**	**Lamivudine 100 mg n=313**	**Difference Entecavir - Lamivudine (95% CI)**
ALT normalization (≤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] (log10 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[f] (%)	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 detected in 42% of individuals treated with entecavir and 25% of individuals treated with lamivudine (p<0.0001) in Study A and 74% of individuals treated with entecavir and 62% of individuals treated with lamivudine (p = 0.0013) in Study B.
[e] Quantiplex bDNA assay.

[f] p<0.01
CI = confidence interval.

Patient responses with a baseline Knodell Fibrosis Scores of 4 (cirrhosis) were equivalent to general responses on all efficacy outcome measures (all individuals had compensated liver disease). Histologic Improvement was separate of HBV DNA or ALT levels baseline.

A steady genomic form of nuclear HBV DNA that operates as a hepatic reservoir of the virus is covalently closed circular deoxyribonucleic acid (cccDNA), which delivers the HBV transcription template, and supports viral persistence and relapse. For a subgroup of individuals with paired liver samples in Study A, the mean change from baseline in hepatic cccDNA at week 48 was -0.9 log10 copies/human genome equivalents (approximately 8-fold reduction) and -0.7 log10 copies/HGEq (approximately 5-fold reduction) for entecavir-treated patients (n=159) and lamivudine-treated patients (n=146), respectively. In Study B (AI463027), the mean change from baseline for both treatment groups in hepatic cccDNA at week 48 was -0.5 log10 copies/HGEq (approximately 3-fold reduction) (n=107 and n=1004 for entecavir and lamivudine-treated individuals, respectively).

Outcomes Beyond 48 weeks

HBeAg-positive

Over 96 weeks, it was demonstrated that continuous entecavir therapy (n=354) through accumulative confirmed outcomes for HBeAg-positive patients (everyone treated) resulted in an escalation of the patient amount with HBV DNA < 300 copies/mL by PCR (80%) and ALT normalisation (≤1 times ULN) (87%). Through the final observation on or off therapy, 31% of patients treated with entecavir had HBeAg seroconversion and 5% had HBsAg loss. In the lamivudine therapy group (n=355), accumulative confirmed outcomes results in 39% of individuals with HBV DNA < 300 copies/mL by PCR and 79% of ALT normalization where 26% of subjects had HBeAg seroconversion and 3% had HBsAg loss. The variance between the groups were statistically significant for the percentage of patients with HBV DNA < 300 copies/mL and ALT normalization (p<0.01).

At the completion of treatment dosing, patients who sustained therapy beyond 52 weeks (median of 96 weeks), 74% of entecavir treated patients (n=243) and 37% of lamivudine treated patients (n=164) had HBV DNA < 300 copies/mL by PCR while ALT normalization (≤ 1 times ULN) followed in 79% and 68% of entecavir and lamivudine-treated patients, respectively.

HBeAg-negative

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

For patients whom continued therapy further than 52 weeks (median 96 weeks), 26 (85%) entecavir and 28 (57%) lamivudine-treated individuals had HBV DNA <300 copies/mL by PCR at end of dosing. At the end of dosing, ALT normalization (≤ 1 times ULN) followed in 27% of entecavir and 21% of lamivudine-treated individuals.

Liver Biopsy Results

In the two nucleoside-naïve trials, 293 of the 679 entecavir monohydrate-treated eligible patients (43%) registered in a long-term rollover study continued entecavir monohydrate treatment. In the rollover trial, individuals received entecavir monohydrate 1 mg once per day. 69 of the 293 patients (26%) selected to have a duplicate liver biopsy after a duration of more than 144 weeks of total treatment (3 years). 57 patients (19%) had both an evaluable

baseline and long-term biopsy, with a median entecavir monohydrate therapy duration of 280 weeks (about six years). 96% of these individuals had Histologic Improvement (a ≥ 2-point reduction in Knodell necroinflammatory score from baseline with no deterioration of the Knodell fibrosis score), and 88% had a ≥1-point reduction in Ishak fibrosis score. Of the 43 individuals with a baseline Ishak fibrosis score of ≥2, 58% had a ≥ 2-point reduction. All individuals (10/10) with advanced fibrosis or cirrhosis at baseline (Ishak fibrosis score of 4,5 or 6) had a ≥ 1 point reduction (median reduction from baseline of 1.5 points). At the moment of the long-term biopsy, 57 (100%) and 49 (86%) of patients had HBV DNA < 300 copies/mL and serum ALT ≤1 X ULN, respectively.

Lamivudine-Refractory Patients
Outcomes at 48 weeks
A Phase 3 Study C (AI463026) was a randomised, multinational, double-blind trial in 286 (of 293 randomised) patients with lamivudine-refractory chronic hepatitis B infection were treated with entecavir. Individuals who received lamivudine at the start of the trial either converted to entecavir 1 mg once per day or remained on lamivudine 100 mg over 52 weeks. The ethnic distribution was 37% Asian and 62% Caucasian, with a mean age of 39 years (range 16 to 74). At baseline, 85% had LVDR mutations. Patients had mean serum HBV DNA levels as measured by Roche COBAS Amplicor® PCR assay of 9.36 log10 copies/mL, a mean Knodell Necroinflammatory Score of 6.5, and a mean serum ALT level of 128 U/L. At week 52, response was evaluated on the basis of test results collected at the week 48 visit. 98% of patients had a baseline liver biopsy, with 88% having a biopsy at week 48 with paired samples collected for 87% of individuals.

In the Phase 3 Study C (AI463026) C, entecavir was better than lamivudine on the Histologic Improvement coprimary endpoints (using the Knodell Score at week 48) and the Composite Endpoint (the quantity of patients with HBV DNA <0.7 MEq/mL by bDNA assay and ALT <1.25 ULN at week 48). Table 12 shows these outcomes and variations in the Ishak Fibrosis Scores. Table 13 demonstrates the biochemical, serologic, and virologic, endpoints for the Phase 3 Study C.

Table 12: Histologic Improvement and Change at Week 48 in Ishak Fibrosis Score, Lamivudine-Refractory Patients in Phase 3 Study C (AI463026)

	Entecavir 1 mg n=124[a]	**Lamivudine 100 mg n=116[a]**	**Difference Entecavir-Lamivudine (97.5% CI)**
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	
Deteriorating[e] (%)	11	26	
Unsatisfactory Week 48 biopsy (%)	2	1	
Missing Week 48 biopsy (%)	10	15	

Composite Endpoint[h] (%)	**n=141** 55	**n=145** 4	50.5[d] (40.4, 60.6)

[a] Individuals 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] Missing or unsatisfactory biopsies at week 48 were classified "no improvement."
[d] p<0.0001.
[e] For Ishak Fibrosis Score, improvement = ≥1-point reduction from baseline and deteriorating = ≥1-point increase from baseline.
[f] p<0.01.
[g] 95% confidence interval (C.I).
[h] Composite Endpoint (a coprimary endpoint) was described as HBV DNA <0.7 MEq/mL by bDNA assay and serum ALT (<1.25 X ULN) at Week 48.
CI = confidence interval

Table 13: Biochemical, Serologic, and Virologic Endpoints at Week 48, Lamivudine-Refractory Patients a Phase 3 Study C (AI463026)

	Phase 3 Study Study C (AI463026)		
	Entecavir 1 mg n=141	**Lamivudine 100 mg n=145**	**Difference Entecavir-Lamivudine (95% CI)**
ALT normalization (≤1 x ULN) (%)	61	15	45.8[b] (35.9, 55.8)
HBV DNA			
Mean change from baseline by PCR[b] (log10 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 detected in 7% of individuals treated with entecavir and no individuals treated with lamivudine (p=0.0011) in Study C (AI463026) and 12% of individuals treated with entecavir and 2% of individuals treated with lamivudine (p= 0.0749) in a Phase 2 Study D (AI463014).
[d] Quantiplex bDNA assay.
CI = confidence interval.

The results for individuals in Study C (AI463026) with a baseline Knodell Fibrosis Scores of four (cirrhosis) were equivalent to the inclusive results on all efficacy result measures (all individuals had compensated liver disease). Histologic Improvement was separate of the ALT or baseline HBV DNA levels.

For a group of individuals with paired liver samples, the mean variation from baseline in hepatic cccDNA at week 48 was -0.6 log10 copies/HGEq (around a 4-fold decrease) and 0.0 log10 copies/HGEq for entecavir (n=74) and lamivudine-treated patients (n=59), respectively.

In Study C (AI463026) the health-related quality of life (HRQoL) was assessed using the

regulated and validated EQ-5D instrument developed by the EurolQol group. Following 48 weeks of treatment, individuals who were placed on entecavir therapy experienced significantly less deterioration in comparison to the lamivudine-treated individuals in the dimensions of self-care, mobility, and pain/discomfort.

Outcomes beyond 48 weeks

The optimum therapy duration with entecavir is not known. In accordance to mandated criteria protocol in the Phase 3 clinical studies, individuals withdrew from entecavir or lamivudine therapy following 52 weeks corresponding to a response definition based on HBV virologic suppression (<0.7 mEq/mL by bDNA assay) and either loss of HBeAg in HBeAg-positive individuals, or ALT <1.25 X ULN in HBeAg-negative individuals at week 48. Patients who attained virologic suppression but did not achieve serologic response (HBeAg-positive) or did not reach ALT <1.25 X ULN (HBeAg-negative) continued treatment with blinded dosing until 96 weeks or until the response guidelines were met. The specific protocol subject management criteria are not proposed as guidance for clinical practice.

Nucleoside-naïve HBeAg-positive
In a Phase 3 Study A (AI46022), amongst nucleoside-naïve HBeAg-positive individuals, 69% (243/354) of patients treated with entecavir and 46% (164/355) of patients treated with lamivudine continued treatment with blinded dosing for up to 96 weeks. Of those individuals continuing with blinded treatment in year 2, 74% (180/243) of patients treated with entecavir and 37% (60/164) of patients treated with lamivudine attained HBV DNA <300 copies/mL by PCR at the end of dosing. 79% (193/243) of patients treated with entecavir attained ALT ≤1 X ULN in comparison to 68% (112/164) patients treated with lamivudine. The amount of individuals with a virologic response but not serologic response who attained a loss of HBeAg at the end of treatment in the year 2 of blinded treatment was 15% (37/243) for entecavir and 17% (28/164) for lamivudine. The quantity who attained HBeAg seroconversion was 11% (26/243) for entecavir and 12% (20/164) for lamivudine.

Post-treatment follow-up: Amongst nucleoside-naïve HBeAg-positive individuals, 31% (111/354) of patients treated with entecavir and 26% (93/355) of patients treated with lamivudine encountered the response definition at the end of dosing, withdrew from the study drugs, and were followed off-treatment for up to 24 weeks. In this group, 31% (34/111) of individuals treated with entecavir and 29% (27/93) of patients treated with lamivudine had HBV DNA <300 copies/mL by PCR at the end of follow-up. At the conclusion of follow-up, 70% (78/111) of the entecavir cohort and 63% (59/93) of the lamivudine cohort recorded ALT ≤1 X ULN.

Nucleoside-naïve HBeAg-negative
Amongst nucleoside-naïve, HBeAg-negative individuals (Phase 3, Study B (AI463027), 8% (26/325) of individuals treated with entecavir and 9% (28/313) of patients treated with lamivudine continued with blinded therapy for up to 96 weeks. In the groups continuing therapy, 85% (22/26) participants treated with entecavir and 57% (16/28) treated with lamivudine had HBV DNA <300 copies/mL by PCR and 7 and 6 entecavir-treated and lamivudine-treated patients, respectively, had ALT ≤1 X ULN at the end of dosing (up to 96 weeks).

Post-treatment follow-up: Amongst the nucleoside-naïve, HBeAg-negative patients, 88% (286/325) were treated with entecavir and 81% (253/313) were treated with lamivudine who met the response definition at the end of dosing therapy, in which they withdrew from the study drugs and were monitored off-treatment for up to 24 weeks. In this group, 2% (7/286) patients that were treated with entecavir and 4% (10/253) of patients treated with lamivudine

had HBV DNA <300 copies/mL by PCR at the end of follow-up. At the end of follow-up 45% (129/286) in the entecavir cohort and 34% (85/253) in the lamivudine cohort recorded ALT ≤ 1 X ULN.

Results of Liver Biopsy
57 individuals from the pivotal nucleoside-naïve Phase 3 trials Study A (AI463022) (HBeAg positive) and Study B (AI463027) (HBeAg negative) who registered in a long-term rollover trial were monitored for long-term liver histology results. All patients (100%) had both an evaluable baseline and long-term biopsy, with a median period of of entecavir treatment of 280 weeks (about six years).

96% (55/57) of these individuals had Histologic Improvement (a ≥2-point reduction in Knodell necroinflammatory score from baseline with no deterioration of the Knodell fibrosis score), and 88% (50/57) had a ≥1-point reduction in Ishak fibrosis score. Of the 43 patients with a baseline Ishak fibrosis score of ≥2, 58% 25/43 had a ≥2-point reduction. All (10/10) individuals with advanced fibrosis or cirrhosis at baseline (Ishak fibrosis score of 4.5 or 6) had a ≥1-point reduction (median reduction from baseline of 1.5 points). At the point of the long-term biopsy, 100% 57/57of patients had HBV DNA <300 copies/mL and 86% 49/57 had serum ALT ≤1 X ULN.

Lamivudine-Refractory
Among participants of the lamivudine-refractory Phase 3, Study C (AI463026), 55% (77/141) in the group treated with entecavir and 2% (3/145) of the group treated with lamivudine remained on blinded treatment for up to 96 weeks. In the group treated with entecavir, 40% (31/77) attained HBV DNA <300 copies/mL, 81% (62/77) had ALT ≤ 1 X ULN and 10% (8/77) established HBeAg serocoversion at the end of dosing.

Follow-up post-treatment: Of 16% (22/141) of lamivudine-refractory individuals who achieved the response criteria (HBV DNA <0.7 mEq/mL on bDNA assay and loss of HBeAg) while on entecavir therapy, 23% (5/22) had HBV DNA <300 copies/mL by PCR and 55% (12/22) had ALT ≤1 X ULN at the end of follow-up.

Outcomes of Long-term Follow-up Study

A Phase 4 Study E (AI463080) was a global, randomised, open-label, observational, study to measure the long-term benefits and risks of entecavir (0.5 mg/day or 1 mg/day) therapy in comparison to other hepatitis B virus standard of care nucleos(t)ide analogues (nucs) in individuals with chronic HBV (CHB) infection.

A total of 12,378 individuals with CHB had ETV therapy (n=6,216) or other standard of care HBV nucleoside (acid) therapy (non-ETV) (n=6,162). The patients were monitored at baseline and consequently twice per year (every six months) on clinical outcome events (COEs) for up to ten years during the trial. The main COEs evaluated in the trial were overall malignant neoplasms, non-HCC malignant neoplasms, liver-related HBV disease progression, non-HCC HBV disease progression, HCC, and fatalities (including liver-related deaths). The trial information exhibited that ETV was not significantly related with an increased risk of malignant neoplasms in comparison to the application of other standard of care HBV nucs, as evaluated by either the composite endpoint of overall malignant neoplasms or the individual endpoint of non-HCC malignant neoplasm. The most frequent reported malignancy was HCC and then gastrointestinal malignancies with colorectal and gastric cancers being the next most common observed tumour types within the gastrointestinal system in both ETV and non-ETV groups. The information also indicated that long-term ETV use was not related with a lesser occurrence of HBV disease development or a lower rate of overall death.

There were significant changes to the population throughout the long-term follow-up phase and more regular post-randomisation treatment variations in the non-ETV group were reported. The trial was underpowered to show a variance in the non-HCC malignancy rate because of the overall lower than expected background rate. Table 14 shows the principal COE assessment.

Table 14: Principal Analyses or Time to Adjudicated Events – Randomised Treated Individuals

	Number of Subjects with Events			
Endpoint[a]	**ETV (n=6,216)**	**Non-ETV (n=6,162)**	**Hazard Ratio [ETV:Non-ETV] (CI)[b]**	**P-value[c]**
Primary endpoints				
Overall malignant neoplasm (%)	331 (5)	337 (5)	0.93 (0.800, 1.084)	0.3553
Liver-related HBV disease progression (%)	350 (6)	375 (6)	0.89 (0.769, 1.030)	0.1182
Death	238 (4)	264 (4)	0.85 (0.713, 1.012)	0.0676
Secondary endpoints				
Non-HCC malignant neoplasm (%)	95 (2)	81 (1)	1.10 (0.817, 1.478)	
HCC	240[d] (4)	263 (4)	0.87 (0.727, 1.032)	
Liver-related death	46	48	0.91 (0.608, 1.365)	

[a] Overall, malignant neoplasm is a compound event of HCC or non-HCC malignant neoplasm. Progression of Liver-related HBV disease is a compound event of liver-related death, HCC, or non-HCC HBV disease progression.
[b] 95.03% CI for complete 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 eliminated from the analysis.
CI = confidence interval; n = total number of patients.

Special Populations

Decompensated Liver Disease Patients

A Clinical Study F (AI463048) was completed that was open-label and randomised, of entecavir vs. adefovir dipivoxil. In 98% (191 of 195 randomised) individuals with HBeAg-positive or –negative chronic HBV infection and an indication of hepatic decompensation, defined as Child-Turcotte-Pugh (CTP) score of 7 or more, subjects were either HBV-treatment naïve or pre-treated (without pre-entecavir treatment, adefovir dipivoxil, or tenofovir disoproxil fumarate). At baseline, individuals had a mean serum HBV

DNA by PCR of 7.83 log10 copies/mL and mean ALT level of 100 U/L; 54% of individuals were HBeAg-positive; and 35% had a genotypic evidence of resistance to lamivudine. 8.6 was the baseline mean CTP score. The entecavir dosage in this trial was 1 mg once per day. At week 24, entecavir had a better result than adefovir dipivoxil on the primary efficacy endpoint of mean change from baseline in serum HBV DNA by PCR. Table 15 shows the outcomes for selected study endpoints at weeks 24 and 48.

Table 15: Selected Study Endpoints at Weeks 24 and 48, Individuals with Decompensated Liver Disease, Study F (AI463048).

	Week 24		Week 48	
	Entecavir 1 mg (n=100)	**Adefovir Dipivoxil 10 mg (n=91)**	**Entecavir 1 mg (n=100)**	**Adefovir Dipivoxil 10 mg (n=91)**
HBV DNA[a]				
Proportion undetectable (<300 copies/mL) (%)	49*	16	57*	20
Mean change from baseline (log10 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) (%)	59 (46/78) *	39 (28/71)	63 (49/78)*	46 (33/71)
Albumin (≥1 X LLN) (%)	24 (20/82)	20 (14/69)	39 (32/82)	29 (20/69)
Bilirubin (≤1 X ULN) (%)	16 (12/75)	15 (10/65)	20 (15/75)	28 (18/65)
Prothrombin time (≤1 X ULN) (%)	9 (9/95)	7 (6/82)	8 (8/95)	9 (7/82)

[a] Roche COBAS Amplicor® PCR assay (LLOQ = 300 copies/mL).
[b] Defined as a reduction 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 are individuals with irregular values at baseline.
* $p<0.05$
ULN = upper limit of normal, LLN = lower limit of normal

Co-infected Patients with HIV/HBV

A Clinical Study G (AI463038) was a double-blind, randomised, placebo-controlled trial of entecavir versus placebo in 68 individuals co-infected with HBV and HIV who were lamivudine refractory (undergone HBV viremia recurrence whilst obtaining a lamivudine-containing HAART [highly active antiretroviral therapy] treatment). Subjects continued their lamivudine-containing HAART treatment (lamivudine dose 300 mg per day) and were allocated to add either the cohort entecavir 1 mg once per day (51 patients) or

placebo (17 patients) for 24 weeks ensued by an open-label study phase for an extra 24 weeks where all individuals were given entecavir. Participants had a mean serum HBV DNA level by PCR of 9.13 log10 copies/mL, at baseline. At baseline, most individuals were HBeAg-positive, with a mean baseline ALT level of 71.5 U/L. Table 16 shows the week 24 biochemical and virologic endpoints.

Table 16: Week 24 Biochemical and Virologic Endpoints, Study G (AI463038)

	Entecavir 1 mg[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 (log10 copies/mL)	-3.65	+0.11	-3.75[c] (-4.47, -3.04)
ALT normalization (≤1 x ULN)[d] (%)	34	8	26.0[e] (3.8, 48.1)

[a] All individuals also were given a lamivudine-containing HAART treatment.
[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 week 48, the open-label phase, the mean variation from baseline HBV DNA by PCR for individuals initially allocated to entecavir was -4.20 log10 copies/mL. 8% of individuals had HBV DNA <300 copies/mL by PCR; and 37% of individuals with abnormal ALT at baseline had ALT normalization (≤1 times ULN). Entecavir has not been assessed in HIV/HBV co-infected individuals who are not concomitantly taking effective HIV treatment (refer to Section 4.4 – Special Warnings and Precautions of Use - Co-infection with HIV).

Recipients of Liver Transplant

A study assessed the safety and efficacy of entecavir 1 mg once per day in an open label, single-arm, trial in 65 liver transplant patients, (who received a liver transplant due to complications of chronic HBV infection) had an HBV DNA <172 IU/mL (approximately 1000 copies/mL) at the time of the liver transplant. The ethnicity breakdown was 39% Caucasian, and 37% Asian, with 82% male. The mean age was 49 years; with 89% of individuals having HBeAg-negative disease at the moment of transplant. Of the 61 subjects who were able to be evaluated for efficacy (had taken entecavir for at least one month), 60 also were given hepatitis B immune globulin as a piece of the post-transplant prophylaxis treatment. At post-transplant, (week 72), no evaluable individuals had a recurrence of HBV [defined as HBV DNA ≥50 IU/mL (approximately 300 copies/mL)] by last-observation-carried forward investigation. The nature and frequency of adverse events in this trial was constant with those predicted in individuals who had received a liver transplant and the known entecavir safety profile.

5.2 Pharmacokinetic properties

Absorption - In healthy individuals, entecavir absorbed rapidly with peak plasma concentrations appearing between 30 minutes and 1.5 hours. Following various entecavir doses varying between 0.1 mg and 1 mg, there was a dose-proportionate increase in the

values of peak plasma concentration (C_{max}) and the area under the concentration-time curve (AUC). After six to ten days, steady-state was achieved from once per day dosing with around 2-fold accumulation. C_{max} and (C_{trough}) trough plasma concentration for a 0.5mg dose at steady-state were 4.2 ng/mL and 0.3 ng/mL, respectively, and for a 1mg dose, were 8.2 ng/mL and 0.5 ng/mL, respectively. In healthy individuals, the bioavailability of the entecavir tablet was 100% compared to the oral solution.

A minimal absorption delay was recorded following the oral administration of entecavir (0.5 mg) with a typical high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) with 1 to 1.5 hours after a meal versus 0.75 hour on an empty stomach. A reduction in C_{max} and AUC (44-46% and 18-20%, respectively) was recorded (refer to Section 4.2 – Dose and Method of Administration).

Distribution – For entecavir, the predicted volume of distribution was in excess of total body water, proposing that it has effective penetration into tissues. Approximately 13% was recorded for protein binding to human serum protein *in vitro*.

Metabolism - Entecavir is not an inducer, substrate or inhibitor of the CYP450 enzyme system. Concentrations of approximately 340 times higher than those seen in humans, showed that entecavir did not stimulate human CYP450 enzymes 1A2, 2C9, 2C19, 3A4, 3A5 and 2B6. Concentrations of approximately 10,000 times higher than those seen in humans, showed that entecavir did not inhibit any of the significant human CYP450 enzymes 1A2, 2C9, 2C19, 2D6, 3A4, 2B6, and 2E1. No acetylated or oxidative metabolites and minimal amounts of phase II metabolites glucuronide and sulfate conjugates were detected following 14C-entecavir administration in humans and rats.

Excretion - Following peak levels being reached, the plasma concentrations of entecavir reduced in a bi-exponential manner. The terminal elimination half-life was approximately 128 to 149 hours. The drug accumulation index detected with once per day dosing is approximately 2-fold, which implies an applicable accumulation half-life of approximately 24 hours.

Entecavir is primarily eliminated by the kidney. Urinary recovery of unchanged entecavir at steady state ranged between 62% to 73% of the dose. Renal clearance of entecavir is separate from dose with a range between 360 and 471 mL/min which suggests it undergoes glomerular filtration and net tubular secretion.

Special Populations

Gender/ethnicity
The entecavir pharmacokinetic profile does not differ by gender or ethnicity.

Elderly
The entecavir pharmacokinetic profile does not differ by patient age.

Renal impairment
The entecavir pharmacokinetics profile after an individual 1 mg dose were examined in patients (that did not have chronic hepatitis B infection) with various levels of renal impairment, including individuals where their renal impairment was controlled by haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Outcomes are shown in Table 17.

Table 17: Pharmacokinetic Parameters in Subjects with Various Levels of Renal Function

	Renal Function Group					
	Baseline Creatinine Clearance (mL/min)					
	Unimpaired >80 (n=6)	**Mild >50-≤80 (n=6)**	**Moderate 30-50 (n=6)**	**Severe <30 (n=6)**	**Severe *Managed with 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.

In individuals with a creatinine clearance of <50 mL/min, an adjustment to the dosage is recommended, this includes patients on CAPD or haemodialysis. (refer to Section 4.2: Dose and Method of Administration - Renal Impairment).

Following an individual entecavir dose of 1 mg, haemodialysis eliminated about 13% of the entecavir dose over four hours and CAPD eliminated about 0.3% of the entecavir dose over seven days. Entecavir must be given only following haemodialysis.

Hepatic impairment
The entecavir pharmacokinetics following an individual 1 mg dose was reviewed in individuals (minus chronic hepatitis B infection) with moderate and severe hepatic impairment. The entecavir pharmacokinetics were comparable between hepatically impaired patients and healthy control individuals; therefore, no entecavir dosage adjustment is required for hepatically impaired patients.

Post-liver transplant
In HBV-infected liver transplant patients on a steady dose of cyclosporine A or tacrolimus (n=9), the entecavir exposure was about 2-times the exposure in healthy individuals with normal renal function. The entecavir exposure increase was contributed via the changed renal function in these patients. Renal function must be carefully monitored before and throughout entecavir treatment in liver transplant recipients receiving cyclosporine or tacrolimus (refer to Section 4.2: Dose and Method of Administration - Renal Impairment).

Paediatrics
There have been no pharmacokinetic studies completed in children.

Drug Interactions (refer to Section 4.4 – Special Warnings and Precautions of Use - Drug Interactions**)**

Entecavir is not an inhibitor, substrate, or inducer of the CYP450 enzyme system (refer to Section 5.2: Pharmacokinetic Properties - Metabolism and Excretion). The entecavir pharmacokinetics are unlikely to be influenced by the co-administration with substances that

are either induced, metabolised by, or inhibited by the CYP450 system. Furthermore, the pharmacokinetics of recognised CYP substrates are unlikely to be influenced by the co-administration of entecavir.

The steady state of entecavir pharmacokinetics and co-administered medicines were not changed in entecavir interaction studies with each of the following:
- adefovir dipivoxil,
- lamivudine,
- tenofovir disoproxil fumarate.

A pilot study in nine recipients of HBV-infected liver transplants suggests that concurrent cyclosporine A (n=5) or tacrolimus (n=4) treatment did not affect entecavir pharmacokinetics (refer to Section 5.2: Pharmacokinetic Properties - Special Populations, Post-Liver Transplant). The effect of entecavir on the cyclosporine A or tacrolimus pharmacokinetics is not known.

5.3 Preclinical safety data

Carcinogenicity, mutagenesis and impairment of fertility
Carcinogenicity clinical studies on entecavir were conducted over two years with entecavir in rats and mice. Increases in lung tumour frequency in male mice were observed at exposures ≥3 x at 1 mg/day (≥5 times that in humans at 0.5 mg/day). The development of the tumours was preceded by pneumocyte proliferation within the lung. This proliferation was not observed in other species, such as, rats, monkeys, or dogs, which reinforces the conclusion that tumours in the lung observed in mice are species-specific occurrences not pertinent to humans. The frequency of other tumours only increased at the maximum exposures [in mice approximately 40 times at 1 mg/day (approximately 70 times human exposure at 0.5 mg/day) and in rats 35 times (males) and 24 times (females) at 1 mg/day) (62 and 43 times, respectively, human exposure at 0.5 mg/day]. This included brain gliomas in male and female rats, liver carcinomas in male mice, liver adenomas and carcinomas in female rats and benign vascular tumours in female mice. These tumour observations are unlikely to be applicable to humans.

In a mammalian-cell gene mutation assay, an Ames microbial mutagenicity assay, and a transformation assay with Syrian hamster embryo cells, no evidence of genotoxicity was observed. The outcomes were also negative in an oral DNA repair study and an oral micronucleus study in rats. In human lymphocyte cultures, entecavir was clastogenic at approximately 1200 times at 1 mg/day (≥2350 times the C_{max} in humans at 0.5 mg/day).

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

0.5 mg tablet:

Crospovidone
Hypromellose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Opadry white 04F58804

1 mg tablet:
Crospovidone
Hypromellose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Opadry pink 03B14899

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life is 24 months (2 years) from manufacture.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Aluminium blister packs containing 30 tablets.

Not all strengths may be marketed.

6.6 Special precautions for handling and disposal

Not applicable.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

REX Medical Ltd
PO Box 18119
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9 DATE OF FIRST APPROVAL

6 June 2019

10 DATE OF REVISION OF THE TEXT

6 July 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Document	Minor editorial revisions and formatting.
4.6	Carcinogenicity, mutagenesis and impairment of fertility paragraph deleted relocated to section 5.3.
5.3	Carcinogenicity, mutagenesis and impairment of fertility paragraph relocated from section 4.6.